Karyotype Aberrations in Action: The Evolution of Cancer Genomes and the Tumor Microenvironment

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Abstract: Cancer is a disease of cellular evolution. For this cellular evolution to take place, a population of cells must contain functional heterogeneity and an assessment of this heterogeneity in the form of natural selection. Cancer cells from advanced malignancies are genomically and functionally very different compared to the healthy cells from which they evolved. Genomic alterations include aneuploidy (numerical and structural changes in chromosome content) and polyploidy (e.g., whole genome doubling), which can have considerable effects on cell physiology and phenotype. Likewise, conditions in the tumor microenvironment are spatially heterogeneous and vastly different than in healthy tissues, resulting in a number of environmental niches that play important roles in driving the evolution of tumor cells. While a number of studies have documented abnormal conditions of the tumor microenvironment and the cellular consequences of aneuploidy and polyploidy, a thorough overview of the interplay between karyotypically abnormal cells and the tissue and tumor microenvironments is not available. Here, we examine the evidence for how this interaction may unfold during tumor evolution. We describe a bidirectional interplay in which aneuploid and polyploid cells alter and shape the microenvironment in which they and their progeny reside; in turn, this microenvironment modulates the rate of genesis for new karyotype aberrations and selects for cells that are most fit under a given condition. We conclude by discussing the importance of this interaction for tumor evolution and the possibility of leveraging our understanding of this interplay for cancer therapy.

Keywords: aneuploidy; polyploidy; tetraploidy; cancer; karyotype aberrations; tumor microenvironment; tumor ecology; niche construction; tumor evolution

1. Introduction

Cancer has been widely described as a process of Darwinian evolution. In a manner analogous to speciation, cancer cells genomically and phenotypically diverge into distinct populations (often referred to as clones or stem-lines) that coexist in the same tumor [1]. This heterogeneity is further bolstered by sub-clonal variations within these clonal populations [2], much like the heterogeneity observed between individuals of a species in nature. Advances in single cell analysis have provided an unprecedented look into the clonal and sub-clonal architecture of cancer [3] and uncovered considerable intra-tumor heterogeneity (ITH) at multiple biological levels. For example, tumors often show extensive cell-to-cell heterogeneity in epigenetic markers, gene mutations, and chromosome aberrations, as well as spatial heterogeneity in the conditions of the extracellular microenvironment [4–6]. Heterogeneity in one or more of these components can be associated with poor patient outcomes [4–8] and increased probability of disease recurrence [9–13]. Not surprisingly, these forms of heterogeneity underlie marked cell-to-cell heterogeneity in a range of phenotypes, including differences in protein biomarker expression, proliferation, cell and nuclear morphology, immune cell infiltration, motility, metabolism, angiogenic potential, differentiation status, and metastatic potential [14–17].
Cell-to-cell heterogeneity emerges through evolutionary processes, in which new variants are generated by ongoing molecular changes and either survive or are eliminated by natural selection. Epigenetic changes are common in cancer and can occur in response to changes in the extracellular environment or due to perturbations in the cellular machinery that orchestrates epigenetic regulation [18]. For example, mutations or altered expression of genes involved in epigenetic regulation (e.g., regulating DNA methylation, histone modifications, and regulatory non-coding RNAs) can lead to increased rates of epigenetic change (known as epigenetic instability) and epigenetic heterogeneity in tumors [19–25]. Increased rates of mutation at the DNA sequence or chromosomal level, a phenomenon collectively known as genomic instability (GIN), occurs in the vast majority of tumors [26]. The rate of gene mutation can increase due to defective DNA damage repair (mismatch repair, nucleotide excision repair, homologous recombination), DNA replication stress, or structural damage to the chromosomes [8]. Chromosomal abnormalities are also widely observed in tumors [27]. These aberrations emerge through defective chromosome segregation or chromosomal damage (leading to gain or loss of whole or partial chromosomes, known as aneuploidy), or abnormal cell cycle events that lead to genome doubling (polyploidy) [28,29]. Chromosomal instability (CIN) refers to the form of GIN where numerical and/or structural chromosomal aberrations occur at an increased rate.

CIN has been reported as being the most common form of genomic instability in human cancers [30–32], and both CIN and aneuploidy are present in most human tumors [27,33–35]. Despite the complexity involved with untangling the cellular effects of aneuploidy, studies in various model systems have made substantial progress in uncovering how chromosomal aberrations alter cell physiology. In addition to gene-specific effects associated with gain or loss of specific chromosomes or chromosome fragments, aneuploidy and polyploidy in general are associated with a number of cellular effects, including substantial alterations to proliferation rates, cellular metabolism, protein homeostasis, and other phenotypes (reviewed in [36]). Aneuploidy and polyploidy have each been shown to drive tumorigenesis in certain circumstances [37–42]. Large scale chromosome or genome level alterations, such as aneuploidy and polyploidy (hereafter referred to as karyotype aberrations), are expected to have a larger penetrance (i.e., more likely to have a phenotypic effect on the cell) than most sequence-level events [8]. Furthermore, chromosome copy number changes affect a larger portion of cancer genomes than any other form of mutation [43]. Therefore, this review will examine the role of karyotypic heterogeneity (i.e., chromosome copy number heterogeneity) in cancer, as well as the environmental context surrounding karyotype aberrations (for excellent reviews addressing sequence-level and epigenetic heterogeneity, please see [8,18,44,45]).

There is a growing appreciation for the context-dependent (genetic, physiological, environmental, etc.) effects of karyotype aberrations on cell physiology and in cancer (reviewed in [46]). Aneuploid and polyploid cells can cause changes in the cellular and tissue environment [47–49], which may disrupt the normal contextual cues from the local environment that maintain tissue homeostasis. The maintenance of tissue homeostasis serves as a barrier to tumorigenesis [50,51], and deteriorating tissue health may create opportunities for cancer development. Although the importance of genomic and environmental changes in cancer development are generally accepted [7,52], our understanding of the details and ramifications of the interplay between genomic and environmental alterations is far from complete. The goal of this review is to discuss the causes and consequences of karyotype aberrations from the perspective of both the cell and the extracellular environment, and the disastrous impact this may have on the tumor microenvironment (TME) and cancer evolution.
2. Cellular Routes to Karyotype Change

Several mechanisms that can lead to karyotype changes have been well described (reviewed in [28,29]), and include events that can lead to gains and losses of individual chromosomes as well as events that lead to doubling of the genome (Figure 1). Whole genome duplication (WGD) events can occur by a number of different mechanisms, including cell fusion (two cells of the same or different type fuse), cytokinesis failure (a cell proceeds through mitosis, but fails to complete cytokinesis), mitotic slippage (a cell aberrantly exits mitosis without chromosome segregation), and endoreduplication (a cell proceeds through successive S-phases without intervening mitoses) (Figure 1C) [53,54]. The specific route of genome doubling may have different consequences for the cell. For example, mitotic slippage leads to nuclear envelope defects and DNA damage while the other mechanisms are less likely to do so [55]. Newly formed tetraploid cells also inherit extra centrosomes, which can disrupt spindle formation (e.g., leading to multipolar divisions) and kinetochore-microtubule attachments in subsequent divisions [56,57].

Whole chromosome gains or losses generally arise through missegregation of chromosomes in mitosis, leading to an unbalanced inheritance of genomic information by the two daughter cells (Figure 1B, left column). Whole chromosome missegregation can occur via multipolar divisions. While multipolar divisions in tetraploid cells lead to highly aneuploid karyotypes with chromosome counts in between diploid and tetraploid—as observed in tumors [58]—they also lead to a very high likelihood of losing most or all copies of at least one chromosome [59] and daughters of multipolar divisions are rarely viable in cell culture [57,59]. Whole-chromosome missegregation can also occur due to erroneous attachment of the sister chromatids (via the kinetochore) to the microtubules of the mitotic spindle. Such errors include chromosome non-disjunction and anaphase lagging chromosomes. Chromosome non-disjunction occurs when both sister chromatids are segregated into one daughter cell when their kinetochores are both attached predominantly (mero-syntelic attachment) or solely (syntelic attachment) to microtubules from one spindle pole [60–63]. Chromosome non-disjunction may also occur if spindle assembly checkpoint function is compromised and cells enter anaphase with monotelic attachments (one sister kinetochore is attached to a spindle pole while the other kinetochore is unattached) [64,65]. Anaphase lagging chromosomes are another example of chromosome missegregation and they occur when a single kinetochore is attached to microtubules from two spindle poles (merotelic attachment), causing the chromosome to lag behind the other chromosomes in anaphase. Lagging chromosomes may segregate into either daughter cell and rejoin the main chromosome mass before nuclear envelope reformation, resulting in either aneuploidy or euploidy [60,66]. However, lagging chromosomes often lead to the formation of micronuclei, where the nuclear envelope reforms separately around the main chromosome mass and the lagging chromosome(s).

Chromosomes in micronuclei undergo DNA damage at higher rates than chromosomes in the main nucleus [67,68], in part because of defective nuclear envelopes in micronuclei [67,69,70] and erroneous mitotic DNA replication [71]. Chromosomes in micronuclei have been observed to undergo large scale damage (shattering), leading to complex structural re-arrangements of chromosomes in a short time period, a process known as chromothripsis [68,72,73]. Furthermore, a study in PtK1 cells found that chromosomes from micronuclei were more likely than those in the main nucleus to missegregate in the following cell division [74]. Thus, lagging chromosomes can result in no karyotype change, or can lead to whole chromosome aneuploidy, structural aneuploidy, or both. Aneuploidy can also arise due to DNA damage, often accompanied by aberrant DNA repair (Figure 1B, right column). DNA damage can break chromosomes, which can lead to missegregation of chromosome fragments, unbalanced chromosomal translocations, and other partial chromosome copy number changes. Chromatin bridges—a result of chromosome fusion after DNA breaks, telomere dysfunction, or failure to completely replicate or decatenate DNA—often result in structural karyotype aberrations [71,75–79], but can also lead to polyploidy and whole chromosome aneuploidy [79–81]. Along with
lagging chromosomes, chromatin bridges and acentric fragments can give rise to cells with micronuclei, which mark the occurrence of chromosome segregation errors [82,83].

Figure 1. Cellular mechanisms leading to karyotype aberrations. Examples of (A) a normal mitosis and (B) abnormal mitoses leading to the missegregation of whole chromosomes (lagging chromosomes and chromosome non-disjunction; left column), chromosome fragments (right column, right daughter cell), or chromatin bridge-mediated chromosome missegregation (chromatin bridge, right column, left daughter cell; which can give rise to a variety of outcomes, including aneuploidy and tetraploidy [79,84]). Lagging chromosomes, chromatin bridges, and acentric fragments can all give rise to cells with micronuclei. (C) Examples of whole-genome duplication events, including endoreduplication, cytokinesis failure, mitotic slippage, and cell fusion (left to right).
3. Environmental Causes of Karyotype Change

The mechanisms leading to karyotype change discussed above can arise due to spontaneous cellular errors. However, conditions in the extracellular environment can increase the frequency of aberrant mitoses. Various environmental stresses can induce gene mutations or CIN [85–91]. The specific effects of these stresses are modulated by the nature, magnitude, and duration of the stress. Both endogenous (physiological) and exogenous stressors may contribute to genome instability in this way.

Chronic inflammation, which can result from hereditary conditions, diet, and environmental exposure to toxic substances or infectious agents, is a major risk factor for cancer development [92]. Many precancerous lesions (such as Barrett’s esophagus, inflammatory bronchial lesions, and ulcerative colitis) are closely associated with both inflammation and karyotype aberrations [93–95]. Notably, inflammatory factors have been causatively linked to aneuploidy [96–98] and micronucleus formation [99] in some systems. Several mechanistic links between inflammation, DNA damage, and chromosomal aberrations have been reported. One study found that misexpression of activation induced cytidine deaminase (AID), induced by inflammation-mediated NF-κB signaling, can lead to DNA double strand breaks, somatic mutations, and chromosomal aberrations [100]. Several matrix metalloproteases (MMPs) are also increased in inflamed tissue [101], and expression of MMP-3 and MT1-MMP have been linked to increased CIN [102–104]. Furthermore, inflammation can induce epithelial-to-mesenchymal transition (EMT) in cancer cells both by direct action of soluble mediators of cancer-associated inflammation (TGF-β, TNF-α, IL-1β, IL-6, IL-8, CCL2, among others) and by the action of various types of immune cells including M2-activated tumor associated macrophages (TAMs) [105]. It has been shown that cells undergoing EMT can fail cytokinesis and become chromosomally unstable if they fail to arrest [106]. Finally, inflammation can promote genome instability by inducing oxidative stress [101]. Oxidative stress—which may be the product of inflammation or factors such as metabolic dysfunction or radiation [107]—causes damage to various cellular components, including DNA. Oxidative stress is associated with oxidation of DNA bases, induction of DNA double strand breaks, gene mutation, and structural aberrations of the chromosomes [108–112]. Chronic oxidative stress has also been reported to lead to loss of telomere function and, possibly as a consequence, polyploidization [112,113]. Therefore, chronic inflammation and/or oxidative stress can have mutagenic, clastogenic, and aneugenic effects on cells that reside within the inflamed tissue or tumor.

Other extracellular conditions have also been observed to promote genetic or chromosomal changes in cultured cells, including serum starvation, hypoxia, lactic acidosis, irradiation, and exposure to DNA damaging agents [86–88,114–117]. These factors represent stresses that can occur in tissues or tumors under certain conditions but are largely atypical in healthy tissues. A variety of exogeneous biotic and abiotic factors have also been linked with karyotypic changes, including viral infection [118–120] and exposure to chemicals [121,122]. Viruses or mutagenic agents can also lead to gene mutations or gene inactivation, which may be permissive for the proliferation of aneuploid or polyploid cells (such as inactivation of p53) [123,124]. A number of other studies have linked chemical exposure (e.g., bisphenol A (BPA), heavy metals, air pollution) with accelerated telomere attrition [125–127], which promotes chromosome fusions and breakages, polyploidization, and aneuploidy [128,129].

Tissue architecture is critically important for the maintenance of euploidy. Loss of tissue architecture was shown to lead to mitotic errors and aneuploidy in mouse epithelial cells [130]. Total loss of substrate adhesion was also found to promote cytokinesis failure [131], and wound healing is also associated with emergence of tetraploid cells [132]. Interestingly, loss of substrate adhesion was also found to reduce p53 expression [133,134], which may enable the survival of both aneuploid and polyploid cells [135,136]. Aging—one of the most potent risk factors associated with cancer—is associated with deteriorating tissue architecture [137,138], suggesting that one link between aging and cancer could be a loss of some karyotype-protective features found in younger tissues. Indeed, aneuploid
and polyploid cells in the body have been reported to accumulate with age [139–142], although this claim has been disputed [143]. Altogether, these studies show that the body and tissue environment are critical factors in preventing the genesis of abnormal cells and that a number of factors—including aging, chemical exposure, inflammation, and exposure to harmful chemicals or biological agents—can destabilize cellular mechanisms for maintaining genome integrity.

4. Aneuploidy and Polyploidy Can Both Promote and Buffer Karyotypic Heterogeneity

Aneuploidy, karyotypic heterogeneity, and CIN correlate with several parameters of disease progression, including drug resistance [9,144–149], metastasis risk [150–157], and clinical outcome [6,158–163]. While in many cancers the degree of CIN correlates with degree of aneuploidy and karyotypic heterogeneity [164–167], the relationships between CIN, aneuploidy, and heterogeneity can be complicated. Highly aneuploid tumors are sometimes observed in the absence of ongoing CIN and, conversely, tumors displaying CIN are not always highly aneuploid or karyotypically heterogeneous [30]. The rate at which new karyotype aberrations arise is certainly an important piece of the equation for determining the extent of karyotype heterogeneity in a tumor, but it is balanced by the ability of cells to tolerate new karyotypic aberrations and selective pressures from the environment. Therefore, the amount of karyotypic heterogeneity in a population is a function of the rates at which cells with novel karyotypes are generated and eliminated.

For karyotypic heterogeneity to accumulate, cells must tolerate either ongoing or punctuated bursts of mitotic errors. But what determines if a cell will survive and contribute to karyotypic heterogeneity? The type of error that occurs can affect the cellular outcome (Section 2). The ploidy of the cell in which karyotypic aberrations occur is also important for determining their effects. Aneuploidy already established in a mother cell appears to be associated with reduced fitness cost of additional chromosome missegregation (i.e., aneuploidy tolerance) and with more karyotypic variation [168]. In organoids derived from colorectal cancers, the degree of aneuploidy was, indeed, found to correlate with the ability of cells to tolerate mitotic errors and with karyotypic heterogeneity [164]. In a study of paired primary and metastatic cancer cell lines, the amount of karyotypic variation from cell to cell (i.e., “karyotypic divergence”) was higher in the more aneuploid cancer cells [169]. For example, a near-diploid breast cancer trisomic for chromosomes 7 and 10 (modal chromosome number of 48) had one non-clonal chromosome aberration per cell on average with a range from 0–5, whereas a highly aneuploid pancreatic cancer (modal chromosome number of 64) averaged 10 non-clonal chromosome aberrations per cell with a range from 0–26 [169]. Consistently, an analysis of the Mitelman database found that near-triploid tumors displayed more intercellular karyotype variability compared to near-diploid tumors [170]. Similar to aneuploid cells, tetraploid cells are more tolerant of mitotic errors and accumulate more karyotypic heterogeneity than their diploid counterparts in cell culture [171]. Tetraploidy may offset the high fitness cost of chromosome gains and losses by doubling the copy number of each chromosome [172–174]. This aneuploidy tolerance may explain why WGD often occurs in the evolution of tumors with complex karyotypes. In line with this theory, Dewhurst et al. reported that a majority of colorectal cancers with near-triploid karyotypes evolved through a tetraploid intermediate and displayed more genomic complexity than near-diploid tumors [175]. Together, these studies suggest that polyploidy and/or the degree of aneuploidy may increase the margins of viable karyotype variation, or the “permissive zone” for which cancer cell karyotypes can diverge from the modal karyotype and survive (Figure 2).
Aneuploidy and polyploidy increase the ability of cells to tolerate mitotic errors and resulting karyotype aberrations. As populations of diploid cells (A, origin) evolve to become more aneuploid (move up the y-axis), the degree by which novel karyotypes can diverge from the modal karyotype and result in viable cells increases (“permissive zone”, represented roughly by the size of the blue zone at the given height). This would be expected to increase the amount of karyotypic heterogeneity in a cancer cell population and, in turn, its evolutionary potential. (B) Tetraploidy buffers against negative fitness effects caused by aneuploidy. Therefore, near-4N cells are expected to have a larger permissive zone than their near-2N counterparts, which may explain why whole genome doubling increases karyotypic heterogeneity and is a favorable route to complex aneuploid karyotypes.

Another important factor for karyotypic heterogeneity is the rate of chromosome segregation errors. While aneuploidy can provide a fitness advantage under some circumstances [176–178], aneuploidy may also lead to decreased fitness under normal growth conditions [178–180]. High levels of CIN can also lead to decreased cellular fitness and increased cell death, due to the emergence of cells with new and inviable karyotypes [181,182]. A mathematical model predicted that cancer cells will find an optimal chromosome missegregation rate, at which fitness costs due to missegregation and random, possibly detrimental, aneuploidies are balanced by the generation of phenotypic heterogeneity [173,183]. According to this model, if the rate of chromosome missegregation is too high, cell population growth becomes hampered by the frequent birth of daughter cells with inviable karyotypes. Conversely, not having enough CIN results in less karyotypic (and presumably phenotypic) heterogeneity, which reduces the tumor’s evolutionary potential. This model is supported by observations in mice and human tumors. Several clinical studies reported an association between high CIN and poor patient outcomes in several solid tumor types by categorizing patient tumors as either high or low CIN [161,162,184,185]. However, studies using a non-binary classification of CIN in breast tumors found that the highest levels of CIN were associated with improved patient outcomes [186,187]. Similarly, a parabolic relationship between CIN and patient outcome was observed in breast, ovarian, gastric and non-small cell lung cancers, such that tumors with intermediate levels of CIN had the worst prognosis and both low and high levels of CIN corresponded with better patient outcomes [188] (for further discussion on the relationship between CIN and clinical outcome, see [189]). In a mouse model, low-to-moderate levels of CIN were found to promote tumorigenesis, while high levels of CIN suppressed tumor progression [163]. As a result of these observations, it has been proposed that exacerbating CIN beyond a tolerable level may be a viable therapeutic strategy [190], but such an approach should be considered with caution [191,192].

Altogether, these findings suggest that the coupling of an optimal CIN rate with sufficient aneuploidy to tolerate ongoing karyotypic variation appears to create ideal conditions for cancer evolution.
5. The Role of Aneuploidy and Polyploidy in Tumor Niche Construction

For a complete picture of the role of genomic changes in tumor progression, it is important to examine the bidirectional interplay between cancer cells and their environment, in which cells and tissue both determine and modulate the health of the other. This interplay unfolds throughout the evolutionary history of the tumor, molding and shaping both the TME and tumor cells into entities that are distinctly different than those found in normal tissues (Figure 3). This mirrors ecology’s “niche construction concept,” which describes the formation of ecological niches through the continuous interplay between selection of individuals by the environment and the modification of the environment by the individuals [193–195]. Mathematical modeling and experimental observations of natural systems in which niche construction is an acting force demonstrate that it can alter the evolutionary trajectory of populations [194–197] and the spatial patterning of individuals in an environment [195,197–199].

In tumors, niche construction by cancer cells often results in harsh environments, such as areas with low pH (acidosis) and/or oxygen (hypoxia), that may favor the growth of malignant cells over non-malignant cells. As we have discussed, genomic changes may result from perturbations in the environment (Section 3). There is also evidence that aneuploid and polyploid cells actively remodel their local environment and may have an advantage compared to diploid counterparts in stressful conditions [171,178]. These findings along with the widespread nature of aneuploidy and abnormal environmental conditions observed in human tumors hint at a relationship between aneuploidy and tumor niche construction, although much remains to be learned about this possible link. In this section, we will explore this subject further by examining the role of aneuploid and polyploid cells in shaping the TME (Section 5.1) and the role of the TME as a selective force on karyotypically heterogeneous cells in tumors (Section 5.2).

5.1. Environment Remodeling by Aneuploid and Polyploid Cells: Home Is Where You Make It

While changes in the local environment may cause cell stress and genomic alterations, cells can also shape their own environmental niche through complex interactions with other cells, the extracellular matrix (ECM), and the secretion of signaling molecules or metabolites [200,201]. Cancer cells often harbor a myriad of gene mutations, epigenetic modifications, and karyotypic abnormalities that drive tumorigenesis [26], making it difficult to attribute any environmental effects to a specific oncogenic event. To avoid such confounding factors, much of our understanding about the cellular consequences of aneuploidy comes from carefully controlled experiments that use yeast and mammalian cells with single (or few) aneuploidies or induce short pulses of chromosome missegregation by perturbing the mitotic checkpoint. Aneuploid and polyploid cells have been found to exhibit a diverse spectrum of biological changes, including altered cell fitness, metabolism, and gene expression (reviewed in [36,202–204]). While some of the physiological effects associated with aneuploidy may be specific to the loss or gain of a certain chromosome and not others, a number of studies have found that some physiological effects of aneuploidy are independent of the identity of the particular chromosome being gained or lost. These studies have provided various lines of direct and indirect evidence suggesting that the physiological changes brought about by CIN, aneuploidy, or polyploidy are important in shaping the cell’s relationship with its surroundings. Here, we discuss how the known cellular effects of karyotype aberrations, while only one of the important players in tumor formation, may have potent effects on the environment that disrupt tissue homeostasis and contribute to the co-evolution of cancer cells and the TME observed throughout disease progression [50,205].
Figure 3. Bidirectional, cell-environment interplay in tumor niche construction and the genomic evolution of cancer cells. (A) In normal tissues, cells and the environment interact to promote homeostasis by regulating cell growth, division, and other behaviors essential for proper health. Teal circles depict normal diploid cells and beige-colored square indicates a normal, healthy environment. (B) Over time, however, changes—either natural (aging) or from stress (smoking, obesity, inflammation, etc.)—may occur in either the cell or environment that disrupt this homeostasis. Spontaneous cellular errors may lead to genomic changes (red circle) that alter cell physiology and interactions with the environment, through senescence, cell death, or increased production of lactate, reactive oxygen species, and other signaling molecules, initiating the process of niche construction (thin dashed arrow). Alternatively, environmental conditions may change (light orange-colored square) that increase the frequency of mutations and mitotic errors in cells and select for cells with favorable genomic alterations and/or phenotypes (thin dashed arrow). The order of events that begin tumor niche construction can vary, starting from either a cellular or environmental change. (C) As this bidirectional interplay persists, genomic and environmental evolution continue to influence and shape each other. As the environment erodes and is replaced by a pro-tumorigenic one (dark orange-colored square), various stresses (hypoxia, acidosis, nutrient scarcity, etc.) may emerge that exert strong selective forces (thick dashed arrow) and favor the survival of tumor cells with advantageous genomic changes. In turn, the outgrowth of these abnormal cells amplifies their environmental effects (thick dashed arrow), which continue to modify selective pressures for their benefit. This cycle may serve as a destabilizing feedback loop that explains the substantial genomic and environmental alterations and heterogeneity (different colored circles) observed in malignant aneuploid tumors.
5.1.1. The Transmission of ER Stress to Immune Cells Impairs Anti-Tumor Immunity

Aneuploidy has been found to elicit characteristic cellular stress responses regardless of which chromosome is affected. For example, stoichiometric mismatches between subunits of protein complexes that are encoded on different chromosomes can lead to endoplasmic reticulum stress (ER stress) in aneuploid cells [206–208], and this appears to happen regardless of the specific chromosome that is gained or lost in human and yeast cells [206,208]. Cells experiencing ER stress release soluble molecules into the extracellular environment. These cell secretions can, in turn, induce an ER stress response in adjacent stromal cells and alter their behavior [209–211]. In one study, inducing ER stress in cancer cells elicited an ER stress response in macrophages in co-culture, which led to enhanced production of proinflammatory cytokines by the macrophages [210]. Similarly, the transmission of ER stress from cancer cells to dendritic cells led to arginase activation and impaired T cell function [211]. In mice, ER stress in dendritic cells resulted in constitutive XBP1 activation and altered lipid homeostasis, which repressed T cell-dependent anti-tumor immunity and promoted ovarian cancer progression [209]. An analysis of chromosomal alterations in TCGA samples across 32 tumor types found that aneuploidy positively correlated with gene expression associated with ER stress and the unfolded protein response (UPR), but negatively correlated with intra-tumor T cell cytolytic activity [212]. Furthermore, the same study found that inducing aneuploidy in pseudodiploid cancer cell lines and polyploidy (via cell fusion) in mouse embryonic fibroblasts (MEFs) triggered ER stress. Strikingly, exposure of macrophages to conditioned media from these aneuploid cells promoted an immune-suppressive and proinflammatory phenotype [212]. Altogether, these findings suggest that aneuploidy-induced ER stress may play an important role in repurposing the TME to fuel cancer progression, particularly through altering the function and behavior of immune cells in the tumor microenvironment.

5.1.2. Changes in Metabolism and ROS Homeostasis May Contribute to Tumor Acidosis and Inflammation

Metabolic alterations are commonly observed in aneuploid and polyploid cells [180,213–218]. Both aneuploidy and polyploidy lead to increased glycolytic activity and lactate production [215,217–220]. Metabolic byproducts, such as lactate, are thought to be a major contributor to tumor acidification [221]. Therefore, it is plausible that increased lactate production by cells with abnormal karyotypes could promote the acidification of the extracellular environment during tumor formation, but this link has not been experimentally validated in vivo. Acidosis is common in tumors and can have profound effects on the ongoing cell-cell and cell-environment interactions in the TME. Low extracellular pH disrupts immune system interactions with cancer cells, promotes tissue remodeling, invasion, and metastasis [221–224]. Aneuploid yeast, human, and rodent cells in vitro have been reported to harbor numerous other metabolic changes, including increased glutamine uptake, increased production of ammonium and glutamate and altered nucleotide and sphingolipid metabolism [215,216,219,220]. The metabolic composition of tumor interstitial fluid was recently characterized for several murine tumor types and compared to levels in circulating plasma. The composition of the two fluids was found to differ considerably, due to the rates of nutrient influx via circulation, consumption of nutrients and excretion of metabolic byproducts by cells, and the clearing of metabolic waste into circulation [225]. It is not clear how the altered metabolism of aneuploid or polyploid cells may influence the composition of the interstitial fluid, or what functional consequences this may have for tumor evolution. However, given the observations of altered metabolism in cells with karyotype aberrations, this may be an interesting and important question to answer.

Aneuploid and chromosomally unstable cells show increased levels of reactive oxygen species (ROS) [214]. Multiple mechanisms may contribute to the elevated ROS production in aneuploid cells. Ca$^{2+}$ release from the endoplasmic reticulum, which occurs following prolonged activation of the UPR during ER stress, can interfere with the electron transport chain, lower mitochondrial integrity, and increase ROS levels [226,227]. Furthermore,
increases in the number and activity of mitochondria in cells after the induction of CIN may also lead to the accumulation of ROS [214,228,229]. Higher ROS levels are common in the TME and can promote oxidative stress in cancer and stromal cells [230,231]. While oxidative stress is associated with genotoxicity, protein damage, and mitotic errors [232–234], it also affects how cells interact with their surroundings. In cancer-associated fibroblasts (CAFs), for example, oxidative stress leads to excessive production of lactate, ROS, and nitric oxide, which can increase aneuploidy in adjacent cancer cells [235]. Oxidative stress can also induce inflammation, another driver of cancer development, which can cause DNA damage and CIN [101,236]. Inflammation, in turn, can trigger recruitment of leukocytes, such as neutrophils, lymphocytes, dendritic cells, and macrophages [237]. Although an immune response can eliminate cancer cells, these immune cells can also secrete potent growth factors that promote angiogenesis and potentiate cancer progression [238].

5.1.3. CIN, Cell Death, and Senescence: Potent Forces in Tissue Niche Construction

CIN can lead to the birth of cells with reduced fitness and an increase in cell death owing to the inheritance of complex, and sometimes inviable, karyotypes with random aneuploidies. Cell death has been found to cause the release of stimulatory factors that promote the proliferation of nearby cells [239,240], as well as inflammation and immune cell recruitment [241,242]. Indeed, increased proliferation along with increased cell death (i.e., high cell turnover rate) in tumors may signal a more aggressive disease [243,244]. Complex karyotypes and/or micronuclei formation resulting from CIN can also cause cell cycle defects, DNA damage, and/or stress-induced cell senescence [181,182,245]. The latter is especially important to consider, as senescent cells can have powerful effects on the local environment. Senescent cells exhibit a secretory phenotype (known as the ‘senescence associated secretory phenotype’, or SASP), which can be associated with tumor progression [246,247]. Secreted SASP proteins, which include growth-promoting factors, cytokines, and chemokines, have been shown to promote cell proliferation, inflammation, cell differentiation or phenotype switching, tissue remodeling, angiogenesis, and invasion [246,247]. Senescent cells can also help neighboring cells escape immune detection by cleaving cell surface receptors both in Natural Killer (NK) cells and their potential target cells [248,249]. The enrichment of senescent cells at the invasive front compared to the tumor center in breast [181] and papillary thyroid carcinomas [250] suggests that SASP-mediated environmental remodeling may be important for tumor invasion. Furthermore, increased levels of tetraploidy and karyotypic heterogeneity have also been observed at the tumor margins relative to the core [181,251]. Why tumor cell senescence, WGD events, and CIN may occur more frequently at the tumor margins is unclear but could stem from the environmental conditions (and/or the need for environmental remodeling) and interactions between cancer and stromal cells in these regions.

Micronucleus formation due to chromosome missegregation can also trigger inflammatory signaling [156,252,253]. When micronuclei containing missegregated chromosomes rupture, genomic DNA is exposed to the cytoplasm and activates the cGAS-STING pathway, which can lead to non-canonical NF-κB signaling, EMT, and metastasis [156]. This same study also found that cancer cells with a high rate of CIN displayed mesenchymal cell traits, including increased motility, invasiveness, and vimentin expression [156]. Changes in the levels or spatial organization of vimentin, an intermediate filament involved in cell adhesion, in cancer cells can lead to the stiffening of tumor tissues and alter the biomechanical properties of the TME [254–256]. Reducing CIN levels or micronuclear rupture delayed metastasis in aneuploid tumors [156], demonstrating that the environmental effects associated with cGAS-STING activation, chronic inflammation, and altered tissue stiffness—rather than the karyotypic alterations alone—are important for cancer progression in this system. Importantly, these changes are independent of aneuploidy, indicating that lagging chromosomes can contribute to cancer progression and niche construction via micronucleus formation even if the lagging chromosome is ultimately segregated into the correct daughter cell. CIN and micronucleus formation, however, do not always cause
EMT or promote invasive behavior, even if cGAS-STING is active [257]. Similarly, micronucleus formation does not always lead to cGAS activation [258]. One study found that chromatin bridges, but not micronuclei originating from whole chromosomes, activated cGAS, resulting in the spread of inflammatory signaling from cancer cells to stromal cells (fibroblasts and monocytes) in a co-culture model [258]. Therefore, while the effects of CIN and micronucleus formation on EMT and cGAS-STING activation appear context-dependent, both whole chromosome missegregation and chromatin bridges may induce a chronic inflammatory response that fuels tumor progression.

5.1.4. Altered Centrosome Homeostasis Affects Tissue Organization, Invasiveness, and the Cellular Secretome

Karyotypic aberrations have also been associated with altered centrosome homeostasis [54,172,259,260] and, while causation has not been demonstrated experimentally, it has been proposed that aneuploidy may lead to disrupted centrosome homeostasis [261]. Importantly, similar to aneuploidy, extra centrosomes and structural centrosome abnormalities are common features in human malignancies [262]. It has been shown that, in some contexts, extra centrosomes by themselves are sufficient to promote tumorigenesis [263,264]. Extra centrosomes may contribute to cancer progression by promoting CIN and therefore more aneuploidy [56,57]. Besides promoting CIN, extra or abnormal centrosomes can promote behaviors that alter their microenvironment directly. Experimentally induced centrosome structural defects, meant to mimic changes seen in cancer cells, disrupted tissue organization in 3D cultures [265] and increased invasiveness [266]. Furthermore, extra centrosomes have been linked to a secretory phenotype very similar to that observed in senescent cells which increased invasiveness in nearby cells [267]. Finally, tumors derived from the injection of tetraploid cells into mice had high levels of centrosome amplification and high expression of MMPs [37], which modify the ECM and the extracellular surfaces of other cells and increase cellular invasiveness. The full nature of the link between polyploidy and centrosome amplification remains unknown, however, as polyploid cells in culture quickly lose extra centrosomes [57,84,171,266,268].

5.1.5. Aneuploid Stromal Cells May Also Alter the Tumor Microenvironment

Within a tumor, karyotype aberrations are not exclusive to the cancer cells and have been detected in a variety of cell types in the tumor stroma. While it is recognized that cancer-associated stromal cells have distinct phenotypes compared to their normal counterparts, the effects of aneuploidy on stromal cell behavior and their interactions with the TME is less clear. Chromosomal abnormalities and centrosome amplification have been reported in tumor-associated endothelial cells (TECs) as a result of hypoxia-induced oxidative stress, increased ROS production, and excessive pro-angiogenic signaling in the TME [269–271]. Interestingly, aneuploid TECs were morphologically distinct from normal endothelial cells, including differences in nuclear and cell size [270], which could contribute to the structurally abnormal and leaky blood vessels seen in tumors [272,273]. Defective vasculature, leading to inconsistent nutrient delivery and waste removal, is a major cause of hypoxic and acidic environments in tumors. Nevertheless, it remains uncertain to what extent aneuploidy in TECs contributes to these abnormal phenotypes. Some studies reported that CAFs, one of the most abundant stromal cell populations in solid tumors, are diploid and do not acquire genetic changes [274,275], while other studies have reported chromosome and gene copy number alterations in CAFs derived from melanoma, breast, prostate, colorectal, and ovarian cancer [276–280]. Nevertheless, loss of heterozygosity (LOH) due to changes in chromosome copy number or focal deletions in breast cancer CAFs at the genetic loci of EP300, ATM, IL2RB, and IBD5, which play a role in neovascularization, cell adhesion, ECM organization, and immune cell recognition, were associated with higher tumor grade and metastasis [280]. Together, these studies suggest that genomic alterations in TECs and CAFs may be an important feature of a tumor’s ecological landscape and contribute to disease progression.
5.1.6. Environmental Remodeling by Aneuploid and Polyploid Cells—Summary

Together, the observations discussed here show that the diverse physiological effects of aneuploidy, polyploidy and CIN can lead these cells to alter the extracellular environment in various ways (Table 1). Aneuploidy- and/or polyploidy-associated changes in cell physiology include changes in stress response, metabolism, and centrosome homeostasis, each of which can manifest independent of the specific chromosome(s) gained or lost. Various lines of direct and indirect evidence suggest that these changes can contribute to tissue environment remodeling in ways that may influence tumor evolution. In light of these studies, we can theorize that optimal degrees of aneuploidy, CIN, and centrosome amplification may create a perfect storm for tumor evolution by allowing the evolving cell population to explore new karyotypes and phenotypes, and by producing a substantial level of inviable or senescent cells that release stimulatory and pro-tumorigenic factors into the local environment. In doing so, the emergence of more abnormal and aggressive cells may occur while the homeostatic mechanisms of normal tissues may simultaneously be eroded and replaced by a pro-tumorigenic, genome-destabilizing environment (Figure 3). Although we focused our discussion on the effects of aneuploidy in general, genetic, epigenetic, or chromosomal events that affect specific chromosomes, genes, or processes also have the potential to promote tissue remodeling. For instance, cells with oncogenic KRAS mutations have been observed to potently alter their surroundings and mediate cancer progression [281]. HCT-116 cells with trisomy 5 induced a partial EMT phenotype resulting in increased invasive and metastatic behavior, while gains of other chromosomes suppressed these phenotypes [257]. Moreover, specific chromosome arm copy number changes were associated with differences in leukocyte infiltration as well as macrophage polarity, although the cellular basis for these observations is unclear [282]. However, the value of karyotype aberrations in environmental remodeling may be especially relevant in tumor progression as these effects arise from general and common phenomena (aneuploidy, polyploidy, chromosome missegregation) and do not rely on specific aberrations, which may arise much less frequently. Because of the complex nature of cancer biology, it is important that these connections be interrogated with rigorous studies to better understand the role of aneuploid and polyploid cells in shaping the tumor niche(s) that drive tumor evolution.

Table 1. The effects of karyotypically abnormal cells on the TME.

| Experimental System                                      | Cellular Effect(s)                                                                 | Influence of the Cellular Effect(s) on the TME                                                                 |
|----------------------------------------------------------|-----------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|
| • Budding yeast [208]                                    | • Endoplasmic reticulum (ER) stress:                                               | • ER stress can transmit from cell to cell, including from cancer to stromal cells such as macrophages and dendritic cells [209–211]. |
| • HCT-116 and hTERT-immortalized RPE-1 cells with various trisomies and tetrasomies [206] | • Protein aggregates [208].                                                        | • ER stress in dendritic cells can lead to XBP1 activation, altered lipid homeostasis, and repressed T cell-dependent anti-tumor immunity [209]. |
| • CENP-E inhibited HeLa cells [283].                     | • Compromised proteosome and chaperone proteins [206,208].                        | • Aneuploidy positively correlated with gene expression associated with ER stress and unfolded protein response (UPR) and negatively correlated with intra-tumor T cell cytolytic activity [212]. |
|                                                          | • Impaired protein folding [206].                                                 |                                                                                                               |
Table 1. Cont.

| Experimental System | Cellular Effect(s) | Influence of the Cellular Effect(s) on the TME |
|---------------------|--------------------|-----------------------------------------------|
| • Mouse embryonic fibroblasts (MEFs) with Trisomy 1, 13, 16, or 19 [180]. Spindle assembly checkpoint (SAC) deficient MEFs [214]. Trisomic MEFs and chromosomally unstable cancer cell lines [219]. Haploid yeast strains with disomies for each chromosome [220]. HCT-116 and hTERT-immortalized RPE-1 cells with various trisomies and tetrasomies [215]. A near-tetraploid and a near-diploid line of Ehrlich’s ascites tumor [217]. | Altered metabolism: Increased production of lactate, glutamate, and ammonium; increased glucose and glutamine consumption [180,214,219,220]. Altered nucleotide and membrane metabolism [215]. Altered consumption and production of various metabolites [219]. Increased glycolytic activity in near-tetraploid tumor cells compared to near-diploid tumor cells [217]. | Increased lactate is a common cause of acidosis in tumors [284]. Increased lactate production may result in secretion of lactate into the tumor microenvironment. Increased glucose and glutamine consumption may result in their removal from the environment and other metabolic changes may also contribute to differences in the nutrient landscape observed in tumors [225,285]. Low pH in the extracellular environment may suppress anti-cancer immune response [286]. |
| • Spindle assembly checkpoint (SAC) deficient MEFs [214]. MEFs and human primary fibroblasts with downregulated BUB1 and SMC1A [182]. Aurora B inhibited U2OS and HCT-116 cells [287]. Budding yeast with various aneuploidies [208,228]. | Altered reactive oxygen species (ROS) homeostasis and elevated ROS levels associated with aneuploidy and chromosomal instability [182,208,214,228]. | Increased cellular ROS levels may translate to elevated tissue ROS levels, as observed in tumors [230]. Cancer cell-induced oxidative stress in cancer-associated fibroblasts leads to excessive production of lactate, ROS, and nitric oxide, which can be released in the TME and promote aneuploidy in adjacent cancer cells [235]. Oxidative stress can cause inflammation [236], which is a hallmark of cancer [26,237]. |
| • MEFs and human primary fibroblasts with downregulated BUB1 and SMC1A [182]. Nocodazole and Reversine treatment in HCT-116 and hTERT-immortalized RPE-1 cells [181]. Cancer cell lines with high levels of multipolar divisions [57]. DLD-1 and hTERT-immortalized RPE-1 p53-/- cells undergoing multipolar divisions after induced cytokinesis failure [59]. | CIN-associated cell death [57,59,182]. CIN-associated senescence [181,182]. | Cell death can release stimulatory factors to promote proliferation of nearby cells [239,240]. Cell death can promote inflammation and immune cell recruitment [241,242]. The senescence-associated secretory phenotype (SASP) is associated with cell proliferation, inflammation, cell differentiation or phenotype switching, tissue remodeling, angiogenesis, and invasion [246,247]. Senescent cells can help neighboring cells escape immune detection by cleaving cell surface receptors in NK cells and potential target cells [248,249]. |
Table 1. Cont.

| Experimental System                                                                 | Cellular Effect(s)                                                                 | Influence of the Cellular Effect(s) on the TME                                                                                                                                 |
|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| - Various cell lines treated to induce cytokinesis failure, including DLD-1, HCT-116, MCF10A, and hTERT-immortalized RPE-1 and BJ fibroblast cells [57,59,171,266,268]. | - Acquisition of extra centrosomes occurs with whole genome duplication (WGD) [57,59]. Note, other molecular changes may be required for cells to retain WGD-associated extra centrosomes, as they are quickly lost in cell culture [59]. | - Centrosomal defects meant to mimic those seen in cancer disrupted tissue organization in 3D cultures [265].  
  - Extra centrosomes and/or centrosomal defects can promote invasiveness in cells harboring them [266] and in adjacent cells [267].  
  - Extra centrosomes have been linked to a secretory phenotype similar to SASP, known as the extra centrosome-associated secretory phenotype (ECASP) [267]. |
| - Aneuploid colorectal cancer cell lines compared to diploid ones [259].             | - Altered centrosome homeostasis proposed to occur due to aneuploidy (speculation and associational evidence) [259,261]. |                                                                                                                                                                                                                                                                  |

5.2. Rigged Selection? Stress Conditions in the TME May Favor the Growth and Survival of Karyotypically Abnormal Cells

For niche construction to formally be said to occur, two conditions must be met: (1) an entity must engage in some activity to alter the environment and (2) the environmental change must modify the selective forces acting on that entity [197,288]. The TME, shaped by cancer cells throughout tumor evolution, does indeed exert selective pressures on cells that are very different than the forces that dictate cell survival in normal tissues [200]. In this section, we consider how selective pressures exerted by the constructed tumor microenvironment may favor the growth of karyotypically abnormal cancer cells. We also consider the role of stresses originating from outside of the evolving tumor—namely, cancer therapeutic treatments—in driving the actions of natural selection on aneuploid and/or polyploid cells.

5.2.1. Karyotype Aberrations Can Confer Selective Advantage of Cancer Cells in Their Constructed Niches and in the Face of Cancer Therapeutics

Generally speaking, harsh or stressful environments (e.g., acidic, hypoxic, nutrient poor) eliminate cells that cannot tolerate them, allowing the proliferation and survival of those cells that are best adapted to the environment. Aneuploidy may provide a fitness advantage to various cell types under stress [9,289–294]. In some cases, specific aneuploidies may provide a selective advantage in a given environment by affecting the expression of important genes. The loss of chromosome 8p in MCF10A mammary epithelial cells promoted resistance to hypoxic conditions and chemotherapeutic drugs. This effect was attributed to increased autophagy linked to ASAH1 LOH [295]. Although 8p loss was insufficient to induce transformation in MCF10A cells [295], it is commonly lost in human tumors of epithelial origin, which may be partly connected to the number of tumor-suppressor genes in that genomic region [296] as well as its effects on autophagy and lipid metabolism [295]. In human colon epithelial cells, trisomy 7 cells were found to out-compete diploid counterparts under serum starvation [176]. Similarly, the frequency of chromosome 7 copy number changes also increased in response to glucose deprivation and lactic acidosis in HCT-116 colorectal cancer (CRC) cells [297]. In a study using a different CRC cell line, DLD-1 cells harboring either an extra chromosome 7 or 13 showed more robust growth than euploid controls under conditions common in tumors, including hypoxia, nutrient starvation, and chemotherapy [178]. Notably, gain of 7p and 13q occur recurrently in CRCs [298], supporting the notion that these chromosomal changes may provide important contextual (genomic, transcriptional, environmental, etc.) advantages during colon carcinogenesis. In the case of trisomy 7, this karyotypic alteration may be favorable for cells in stressful environments due at least in part to dysregulation and/or amplification of the EGF gene, which can maintain intracellular glucose levels and prevent autophagic cell death [299].
In many cases, the molecular mechanisms underlying the selective advantages of whole chromosome and chromosome arm aneuploidies are more complex (involving multiple genetic loci on different chromosomes) or unclear. For example, only 2 out of 64 chromosome arm alterations (CAAs) that were predictive of chemotherapeutic drug responses across cancer types could be explained by focal deletions of known drug targets [300]. This suggests that most CAAs associated with drug responses likely depend on the interaction of multiple genes across the affected genomic region and/or other interchromosomal genetic interactions. Following the induction of CIN, recurrent aneuploidies were observed in non-small cell lung cancer cells that developed resistance to the topoisomerase I inhibitor Topotecan [192]. The drug-resistant phenotype in this case was not driven by chromosomal alterations affecting the expression of the drug target. Instead, chromosome 6p gain caused the overexpression of resident genes MAPK13 and MAPK14 that encode for p38 kinase subunits, which led to the selective upregulation of a drug efflux pump on chromosome 4q [192]. Direct gain of 4q may not have been favorable in this context because it harbors numerous tumor suppressor genes, indicating that genetic interactions between specific aneuploidies and other chromosomes influence karyotype evolution (as reported in yeast [301]). In a similar study, recurrent aneuploidies were also detected in various cell lines following Mps1 disruption and drug pressure; however, the observed karyotypic changes were unique for each cell line used even when challenged with the same drug [191]. Although the mechanisms underlying resistance were not identified in this study, the unique karyotypic routes to drug resistance across cell types demonstrate there are multiple genomic paths to a given phenotype (drug resistance) and the cell’s genomic and/or epigenetic background is an important factor for the observed effects of chromosomal alterations.

There is also evidence that WGD can protect normal and cancer cells from stresses in the environment, including energy depletion, oxidative stress, and chemotherapy [171,302–305]. Polyploidy may be a major driver of treatment failure, tumor relapse, and drug-induced genomic evolution [306]. Multiple studies found that giant multi-nucleated polyploid cells arise in vitro and in vivo following drug exposure [307–309]. These polyploid cells may enter a reversible senescent-like state or slow cell cycle progression in response to drug treatment. While many of these cells may permanently arrest or perish [307], on some occasions, they undergo asymmetric, reductive divisions that produce mononuclear cells, which are often aneuploid and highly tumorigenic [310–312]. Furthermore, tetraploidy increased the resistance of non-transformed RPE-1 cells and HCT-116 CRC cells to a variety of chemotherapeutic drugs [171]. The effects of WGD may depend on the genetic background and/or mechanism of tetraploidization, as drug-induced mitotic slippage in PC9 lung cells did not promote resistance to the EGFR inhibitor gefitinib [191]. WGD can also render cells vulnerable to specific genetic challenges, such as impairment of DNA replication, proteasome inhibition, and KIF18A depletion [313]. Highly aneuploid cells (both WGD- and WGD+) were also more dependent on KIF18A compared to less aneuploid or euploid counterparts [314], indicating that KIF18A inhibitors may have immense therapeutic potential.

5.2.2. Karyotypic, Genetic, and Epigenetic Changes Alter Selective Survival of Tumor Stromal Cells

Tumor stromal cells may also acquire important selective advantages through karyotypic changes. Karyotypic complexity and heterogeneity in TECs increased with tumor malignancy [315], and aneuploid TECs were more resistant to anti-angiogenic agents and chemotherapeutic drugs, such as vincristine, paclitaxel, and 5-fluorouracil, than normal endothelial cells [316,317]. Polyploid and aneuploid tumor-associated macrophages (TAMs) have also been detected in the blood of cancer patients [318,319]. By acquiring cancer cell DNA through phagocytosis, TAMs may gain tumorigenic functions that enhance tumor invasion and metastasis [318]. Recent studies found that CAFs isolated from premalignant and malignant skin squamous cell carcinoma were characterized by chromosomal abnormalities and genomic instability [320,321]. Katarkar et al. showed that CAFs with
karyotype aberrations that amplified NOTCH1 suppressed DNA damage-induced ATM signaling and cell cycle arrest in response to UV irradiation, promoting their survival over other CAFs [321]. Therefore, stromal cells with favorable genomic changes can indeed undergo positive selection during tumor progression, and the identification of such events could unlock new stroma-focused anti-cancer intervention strategies. This highlights the need for continued characterization of genetic, karyotypic, and epigenetic alterations in the tumor stroma and their effects on cancer-stromal cell interactions, which may underlie the clinical diversity in treatment response among tumors of the same class and stage [280].

5.2.3. Karyotype Aberrations and Immune Interactions: A Matter of Context

The immune system’s role in eliminating damaged and abnormal cells represents an important selective pressure that cancer cells must overcome. The literature supports the idea that karyotype aberrations can modulate immune cell interactions, although the mechanisms and outcomes appear complicated and context dependent. Aneuploid cells in culture were found to be more susceptible than euploid cells to elimination by NK cells [322]. Similarly, it was shown that polyploid cells could be detected and eliminated by the immune systems of mice [323]. These findings suggest that the immune system may maintain tissue health and protect against cancer by detecting and eliminating aneuploid cells [324]. In humans, however, aneuploidy and polyploidy are associated with reduced immune cell infiltration in tumors, suggesting that aneuploidy may confer cells with a heightened ability to escape immune detection [35,313,325].

The mechanisms relating aneuploidy and immune interactions within tumors are not well understood, as highlighted by recent contrasting observations. One study found that aneuploid cells activated NF-κB signaling to promote their clearance by immune cells, and the NF-κB activity correlated with the degree of aneuploidy in cancer cell lines [326]. In clinical samples, however, highly aneuploid tumors had lower levels of NF-κB activity [35]. This discrepancy suggests that the suppression of NF-κB signaling may result from selective pressures imposed by the TME and represent an important event in the evolution of aneuploid cells in tumors. One explanation may lie in the link between aneuploidy, ER stress, and anti-tumor immunity (Section 5.1.1). ER stress, which is often induced by aneuploidy [206–208], has been associated with the down-regulation of MHC class I-associated peptides [327] and a reduced immune response in cell culture and mouse models [328]. Aneuploidy-induced ER and metabolic stress may also help to create immune suppressive environments through non-cell autonomous mechanisms, as we discussed earlier [212,221,224]. Nevertheless, this proposed mechanism is speculative and based on associative evidence, and further research is needed to directly address these important questions regarding aneuploidy and immune evasion in cancer.

CIN may also help cells overcome immunodetection, although in many cases the exact mechanism is not clear. One study found CIN initially increased tumor cell immunogenicity, consistent with other reports [322,326], but continued evolution under immune selection promotes the proliferation of aneuploid cells that are able to suppress MHC class I antigen presentation and avoid immune detection [329]. A possible mechanism by which CIN and karyotype changes can mediate immune evasion is arm-level or focal deletions on chromosome 6 that result in human leukocyte antigen LOH, which was detected in about 40% of non-small cell lung cancers [330]. Cancer cells with human leukocyte antigen LOH produce less neoantigens and are less susceptible to immune predation, giving them a selective advantage in tumors [330]. Immune evasion, however, can also be achieved by karyotype-independent means. For example, epigenetic silencing of mutated genes (which can generate neoantigens and promote immune clearance of the cells harboring them) or of genes involved in the MHC-I antigen presentation pathway can allow cells to escape destruction by the immune system [329,331].

Immune pressure can dramatically influence clonal selection in tumors [332], leading to the dominance of less immunogenic sub-clones with favorable genomic and epigenetic alterations. Based on the apparent immunogenicity of aneuploid cells [322,323,326,329],
it is tempting to speculate that the physiological consequences of aneuploidy, such as inflammation and the recruitment of immune cells, create a hostile immune predatory environment at first, but through ongoing genomic and environmental evolution a beneficial, immune suppressive TME and/or less immunogenic sub-clones emerge (Figure 3). Further work is needed to elucidate these dynamics through rigorous experimental studies.

5.2.4. Increased Motility in Aneuploid and Polyploid Cells May Provide a Fitness Advantage in Some Contexts

Under certain conditions, motile phenotypes may be advantageous for cells. Mathematical modeling of tumors has shown that there is often a fitness trade-off between proliferation and motility (“go or grow” trade-off) and that it may be advantageous for a cell to be highly motile in certain conditions [333,334]. For example, in rapidly proliferating areas of a tumor, crowding and nutrient scarcity may make it advantageous for a cell to be able to escape such an environment. Thus, karyotypic changes that lead to increased motility could be selected for in or around these areas. Aneuploid cells have been found to be more invasive than diploid counterparts in a protein matrix meant to mimic the ECM [178]. Similarly, near-tetraploid cancer cells exhibited increased migratory and invasive behaviors compared to near-diploid cells [251]. Aneuploidy was also found to play a role in the phenotypic switch known as EMT. This phenotypic switch to the mesenchymal state leads to increased motility and is associated with metastasis [335]. During spontaneous transformation of mouse epithelial cells, aneuploidy arose concurrently with gene expression changes associated with EMT [336]. Another study found that EMT observed in cultured cells was associated with specific, recurrent changes in chromosome content, which affected the expression of ZEB1 and intercellular junction proteins central to the EMT process [337]. There is also in vivo evidence linking aneuploidy to EMT. Across 27 tumor types, the degree of aneuploidy positively correlated with the levels of EMT-related gene expression across 27 tumor types [257]. In addition to aneuploidy per se, it has been reported that chromosome missegregation can also induce EMT to promote invasive and metastatic phenotypes via cGAS-STING activation if micronuclei rupture [338].

5.2.5. Effects of the TME on Karyotypically Abnormal Cells—Summary

Collectively, the findings discussed in this section demonstrate the principle that aneuploidy can provide cells with fitness advantages in certain contexts. Nonetheless, much remains to be uncovered about the interplay between aneuploidy and selective conditions in the complex contexts of tumors. Characteristic patterns of aneuploidy have been reported for different tumor types [339]. It has been proposed that these recurrent aneuploidies might enhance fitness by reinforcing the active transcriptional pathways specific to a given cell type [166,340]. It is also be possible, however, that these cancer-specific aneuploidy patterns are influenced by physiological differences in the tissue environment specific to the anatomical site. For example, a recent pan-cancer analysis of chromosome arm aneuploidies revealed that 7p gain and 10q loss—two recurrent events in primary brain tumors—were enriched in metastases to the brain relative to the primary site [300], suggesting tissue-specific environments may exert selective pressure that define the genomic evolution of tumors at their primary and metastatic sites. It will be important to design organoid and xenograft models to understand how these genome-environment relationships contribute to tumorigenesis.

6. Concluding Remarks

We have discussed how karyotype aberrations arise from cellular errors and environmental conditions; we have also explored the balance of forces that determines the extent of karyotype heterogeneity in a population, and the role of the bidirectional interaction between karyotypically abnormal cancer cells and the environment in shaping the TME and driving tumor evolution. While tremendous progress has been made in understanding how genomic and environmental alterations individually contribute to cancer, continued effort to integrate these fields has the potential to expand our knowledge
of tumor progression. For instance, the role of niche construction in cancer is not well understood, and particularly the role of aneuploidy in niche construction has not been directly addressed to our knowledge. Therefore, many fundamental questions remain open. For instance, does the accumulation of aneuploidy in tumors exacerbate changes in the TME, diversifying tumor ecology across time and space? It seems plausible that the eco-evolutionary interactions that we discuss in this review act in tumors as a feedback loop that bolsters genomic and/or environmental heterogeneity, thereby driving tumor progression. How niche construction alters the spatial patterning of environmental niches and cell populations in tumors, and the consequences of this for disease progression and treatment response is unclear. Recognizing the parallels between species-environment dynamics in natural ecosystems, researchers have begun studying cancer from an ecological perspective and taking systems-level approaches. By integrating data from in vitro and in vivo systems, genomic and molecular analyses, bioinformatics, and mathematical modeling, we hope that these important questions can be answered. Indeed, experimental methods such as laser capture microdissection combined with single cell analyses (LCM-seq) are already being used to gain better understanding of spatial and functional relationships between different cells within a tumor and between cells and specific microenvironmental niches [341]. Such multimodal analyses integrating genomic, transcriptomic, epigenomic, and microenvironmental data are providing new insights into cancer biology [342,343].

Analysis of other complex systems has revealed various “leverage points” at which manipulation leads to amplified effects in the system [344]. Thus, experimental and mathematical analysis of niche construction and related ecological and evolutionary feedbacks in tumors may help to identify the processes central to cancer development, determine the best ways to disrupt the abnormal dynamics at play in cancerous tissue, and either return the system to a less malignant state or push the tumor to the point of collapse. Through a better understanding of the interactions and forces—genomic, environmental, and others—that shape tumor ecosystems, we hope that potent new therapeutic strategies will emerge.

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References
1. Nowell, P.C. The clonal evolution of tumor cell populations. Science 1976, 194, 23–28. [CrossRef] [PubMed]
2. McGranahan, N.; Swanton, C. Clonal heterogeneity and tumor evolution: Past, present, and the future. Cell 2017, 168, 613–628. [CrossRef] [PubMed]
3. Navin, N.E. The first five years of single-cell cancer genomics and beyond. Genome Res. 2015, 25, 1499–1507. [CrossRef]
4. Klughammer, J.; Kiesel, B.; Roetzer, T.; Fortelny, N.; Řenc, A.; Nening, K.-H.; Furtner, J.; Sheffield, N.C.; Datlinger, P.; Peter, N. The DNA methylation landscape of glioblastoma disease progression shows extensive heterogeneity in time and space. Nat. Med. 2018, 24, 1611–1624. [CrossRef] [PubMed]
5. Junnila, M.R.; de Sauvage, F.J. Influence of tumour micro-environment heterogeneity on therapeutic response. Nature 2013, 501, 346. [CrossRef] [PubMed]
6. Friedlander, M.L.; Hedley, D.W.; Taylor, I. Clinical and biological significance of aneuploidy in human tumours. J. Clin. Pathol. 1984, 37, 961–974. [CrossRef]
7. Jamal-Hanjani, M.; Wilson, G.A.; McGranahan, N.; Birkbak, N.J.; Watkins, T.B.; Veeriah, S.; Shafi, S.; Johnson, D.H.; Mitter, R.; Rosenthal, R. Tracking the evolution of non–small-cell lung cancer. N. Engl. J. Med. 2017, 376, 2109–2121. [CrossRef]
8. Burrell, R.A.; McGranahan, N.; Bartek, J.; Swanton, C. The causes and consequences of genetic heterogeneity in cancer evolution. Nature 2013, 501, 338–345. [CrossRef]
40. Sotillo, R.; Hernando, E.; Diaz-Rodriguez, E.; Teruya-Feldstein, J.; Cordón-Cardo, C.; Lowe, S.W.; Benezra, R. Mad2 overexpression promotes aneuploidy and tumorigenesis in mice. Cancer Cell 2007, 11, 9–23. [CrossRef]

41. Baker, D.J.; Jin, F.; Jeg Nathanan, K.B.; van Deursen, J.M. Whole chromosome instability caused by Bub1 insufficiency drives tumorigenesis through tumor suppressor gene loss of heterozygosity. Cancer Cell 2009, 16, 475–486. [CrossRef]

42. Hanks, S.; Coleman, K.; Reid, S.; Plaja, A.; Firth, H.; FitzPatrick, D.; KIDD, A.; MÉHES, K.; Nash, R.; Robin, N. Constitutional aneuploidy and cancer predisposition caused by biallelic mutations in BUB1B. Nat. Genet. 2004, 36, 1159–1161. [CrossRef]

43. Beroukhim, R.; Mermel, C.H.; Porter, D.; Wei, G.; Raychaudhuri, S.; Donovan, J.; Barretina, J.; Boehm, J.S.; Dobson, J.; Urrashima, M. The landscape of somatic copy-number alteration across human cancers. Nature 2010, 463, 899. [CrossRef]

44. Turajlic, S.; Sottoriva, A.; Graham, T.; Swanton, C. Resolving genetic heterogeneity in cancer. Nat. Rev. Genet. 2019, 20, 404–416. [CrossRef]

45. Mazor, T.; Pankov, A.; Song, J.S.; Costello, J.F. Intratumoral heterogeneity of the epigenome. Cancer Cell 2016, 29, 440–451. [CrossRef] [PubMed]

46. Ben-David, U.; Amon, A. Context is everything: Aneuploidy in cancer. Nat. Rev. Genet. 2019, 21, 44–62. [CrossRef] [PubMed]

47. Baker, D.J.; Jeg Nathanan, K.B.; Cameron, J.D.; Thompson, M.; Juneja, S.; Kopecka, A.; Kumar, R.; Jenkins, R.B.; De Groen, P.C.; Roche, P. Bub1R insufficiency causes early onset of aging-associated phenotypes and infertility in mice. Nat. Genet. 2004, 36, 744–749. [CrossRef] [PubMed]

48. Baker, D.J.; Jeg Nathanan, K.B.; Malureau, L.; Perez-Terzic, C.; Terzic, A.; van Deursen, J.M. Early aging-associated phenotypes in Bub3/Rae1 haploinsufficient mice. J. Cell Biol. 2006, 172, 529–540. [CrossRef] [PubMed]

49. Melo Pereira, S.; Ribeiro, R.; Logarinho, E. Approaches towards longevity: Reprogramming, senolysis, and improved mitotic competence as anti-aging therapies. Int. J. Mol. Sci. 2019, 20, 938. [CrossRef]

50. Bissell, M.J. Context matters. Trends Cancer 2015, 1, 6–8. [CrossRef]

51. Bissell, M.J.; Hines, W.C. Why don’t we get more cancer? A proposed role of the microenvironment in restraining cancer progression. Nat. Med. 2011, 17, 320. [CrossRef]

52. Yuan, Y. Spatial Heterogeneity in the Tumor Microenvironment. Cold Spring Harb. Perspect. Med. 2016, 6. [CrossRef]

53. Lee, H.O.; Davidson, J.M.; Duronio, R.J. Endoreplication: Polyploidy with purpose. Cold Spring Harb. Perspect. Med. 2016, 8. [CrossRef]

54. Storchova, Z.; Pellman, D. From polyploidy to aneuploidy, genome instability and cancer. Nat. Rev. Mol. Cell Biol. 2005, 6, 529–540. [CrossRef] [PubMed]

55. Silkworth, W.T.; Nardi, I.K.; Scholl, L.M.; Cimini, D. Multipolar spindle pole coalescence is a major source of kinetochore mis-attachment and chromosome mis-segregation in cancer cells. PLoS ONE 2009, 4, e6564. [CrossRef]

56. Gregan, J.; Polakova, S.; Zhang, L.; Tolic-Norrellykke, I.M.; Cimini, D. Merotelic kinetochore attachment: Causes and effects. Trends Cell Biol. 2011, 21, 374–381. [CrossRef] [PubMed]

57. Baudoin, N.C.; Nicholson, J.M.; Soto, K.; Martin, O.; Chen, J.; Cimini, D. Asymmetric clustering of centrosomes defines the early evolution of tetraploid cells. Elife 2020, 9. [CrossRef]

58. Zack, T.I.; Schumacher, S.E.; Carter, S.L.; Cherniack, A.D.; Saksena, G.; Tabak, B.; Lawrence, M.S.; Zhang, C.-Z.; Wala, J.; Mermel, C.H. Pan-cancer patterns of somatic copy number alteration. Nat. Genet. 2013, 45, 1134–1140. [CrossRef] [PubMed]

59. Baudoin, N.C.; Nicholson, J.M.; Soto, K.; Martin, O.; Chen, J.; Cimini, D. Asymmetric clustering of centrosomes defines the early evolution of tetraploid cells. Elife 2020, 9. [CrossRef]

60. Thompson, S.L.; Compton, D.A. Chromosome missegregation in human cells arises through specific types of kinetochore-microtubule attachment errors. Proc. Natl. Acad. Sci. USA 2011, 108, 17974–17978. [CrossRef] [PubMed]

61. Cimini, D.; Degrassi, F. Aneuploidy: A matter of bad connections. Trends Cell Biol. 2005, 15, 442–451. [CrossRef] [PubMed]

62. Toscanucci, L.; Puzzonia, M.D.S.; Cenciarelli, C.; Rens, W.; Degrassi, F. Aneuploidy in mitosis of PtK1 cells is generated by random loss and nondisjunction of individual chromosomes. J. Cell Sci. 2009, 122, 3455–3461. [CrossRef]

63. Gregan, J.; Polakova, S.; Zhang, L.; Tolić-Norrellykke, I.M.; Cimini, D. Merotelic kinetochore attachment: Causes and effects. Trends Cell Biol. 2011, 21, 374–381. [CrossRef] [PubMed]

64. Canman, J.C.; Sharma, N.; Straight, A.; Shannon, K.B.; Fang, G.; Salmon, E.D. Anaphase onset does not require the microtubule-dependent depletion of kinetochore and centromere-binding proteins. J. Cell Sci. 2002, 115, 3787–3795. [CrossRef]

65. Cimini, D.; More, B.; Canman, J.C.; Salmon, E. Merotelic kinetochore orientation occurs frequently during early mitosis in mammalian tissue cells and error correction is achieved by two different mechanisms. J. Cell Sci. 2003, 116, 4213–4225. [CrossRef] [PubMed]

66. Cimini, D.; Fioravanti, D.; Salmon, E.D.; Degrassi, F. Merotelic kinetochore orientation versus chromosome mono-orientation in the origin of lagging chromosomes in human primary cells. J. Cell Sci. 2002, 115, 507–515.

67. Terradas, M.; Martin, M.; Hernandez, L.; Tusell, L.; Genesca, A. Nuclear envelope defects impede a proper response to micronuclear DNA lesions. Mutat Res. 2012, 729, 35–40. [CrossRef] [PubMed]

68. Zhang, C.Z.; Spektor, A.; Cornils, H.; Francis, J.M.; Jackson, E.K.; Liu, S.; Meyerson, M.; Pellman, D. Chromothripsis from DNA damage in micronuclei. Nature 2015, 522, 179–184. [CrossRef] [PubMed]

69. Liu, S.; Kwon, M.; Mannino, M.; Yang, N.; Renda, F.; Khodjakov, A.; Pellman, D. Nuclear envelope assembly defects link mitotic errors to chromothripsis. Nature 2018, 561, 515–555. [CrossRef]

70. Hatch, E.M.; Fischer, A.H.; Deerinck, T.J.; Hetzer, M.W. Catastrophic nuclear envelope collapse in cancer cell micronuclei. Cell 2013, 154, 47–60. [CrossRef]
71. Umbreit, N. T.; Zhang, C.-Z.; Lynch, L. D.; Blaine, L. J.; Cheng, A. M.; Tourdot, R.; Sun, L.; Almubarak, H. F.; Judge, K.; Mitchell, T. J. Mechanisms generating cancer genome complexity from a single cell division error. *Science* 2020, 368, eaba0712. [CrossRef] [PubMed]

72. Ikehuti, T.; Weinfeld, H.; Sandberg, A. A. Chromosome pulverization in micronuclei induced by tritiated thymidine. *J. Cell Biol.* 1972, 52, 97–104. [CrossRef] [PubMed]

73. Ly, P.; Brunner, S. F.; Shoshani, O.; Kim, D. H.; Lan, W.; Pyntikova, T.; Flanagan, A. M.; Behjati, S.; Page, D. C.; Campbell, P. J. Chromosome segregation errors generate a diverse spectrum of simple and complex genomic rearrangements. *Nat. Genet.* 2019, 51, 705–715. [CrossRef] [PubMed]

74. He, B.; Gnawali, N.; Hinman, A. W.; Mattingly, A. J.; Osimani, A.; Cimini, D. Chromosomes missegregated into micronuclei contribute to chromosomal instability by missegregating at the next division. *Oncotarget* 2019, 10, 2660. [CrossRef] [PubMed]

75. McClintock, B. The stability of broken ends of chromosomes in *Zea mays*. *Genetics* 1941, 26, 234. [PubMed]

76. Cimini, D.; Antoccia, A.; Tanzarella, C.; Degras, F. Topoisomerase II inhibition in mitosis produces numerical and structural chromosomal aberrations in human fibroblasts. *Cytogenet. Genome Res.* 1997, 76, 61–67. [CrossRef]

77. O’Sullivan, J. N.; Bronner, M. P.; Brentnall, T. A.; Finley, J. C.; Shen, W.-T.; Emerson, S.; Emond, M. J.; Gollahon, K. A.; Moskovitz, A. H.; Crispin, D. A. Chromosomal instability in ulcerative colitis is related to telomere shortening. *Nat. Genet.* 2002, 32, 280–284. [CrossRef]

78. Stewénius, Y.; Gorunova, L.; Jonson, T.; Larsson, N.; Höglund, M.; Mandahl, N.; Mertens, F.; Mitelman, F.; Gisselsson, D. Structural and numerical chromosome changes in colon cancer develop through telomere-mediated anaphase bridges, not through mitotic multipolarity. *Proc. Natl. Acad. Sci. USA* 2005, 102, 5541–5546. [CrossRef]

79. Pampalona, J.; Roscioli, E.; Silkworth, W. T.; Bowden, B.; Genescà, A.; Tusell, L.; Cimini, D. Chromosome bridges maintain kinetochore-microtubule attachment throughout mitosis and rarely break during anaphase. *PLoS ONE* 2016, 11, e0147420. [CrossRef]

80. Pampalona, J.; Frias, C.; Genescà, A.; Tusell, L. Progressive telomere dysfunction causes cytokinesis failure and leads to the accumulation of polyploid cells. *PLoS Genet.* 2012, 8, e1002679. [CrossRef] [PubMed]

81. Pampalona, J.; Soler, D.; Genescà, A.; Tusell, L. Whole chromosome loss is promoted by telomere dysfunction in primary cells. *Genes Chromosomes Cancer* 2010, 49, 368–378. [CrossRef] [PubMed]

82. Russo, A.; Degras, F. Molecular cytogenetics of the micronucleus: Still surprising. *Mutat. Res. Genet. Toxicol. Environ. Mutagenesis* 2018, 836, 36–40. [CrossRef]

83. Ye, C. J.; Sharpe, Z.; Alemany, S.; Mackenzie, S.; Liu, G.; Abdallah, B.; Horne, S.; Regan, S.; Heng, H. H. Micronuclei and genome chaos: Changing the system inheritance. *Genes* 2019, 10, 366. [CrossRef] [PubMed]

84. Russo, A.; Pacchierotti, F.; Cimini, D.; Ganem, N. J.; Genescà, A.; Naturalajan, A. T.; Pavanello, S.; Valle, G.; Degras, F. Genomic instability: Crossing pathways at the origin of structural and numerical chromosome changes. *Environ. Mol. Mutagenesis* 2015, 56, 563–580. [CrossRef]

85. Young, S.; Marshall, R.; Hill, R. Hypoxia induces DNA overreplication and enhances metastatic potential of murine tumor cells. *Proc. Natl. Acad. Sci. USA* 1988, 85, 9533–9537. [CrossRef]

86. Goncharova, E. I.; Nádas, A.; Rosman, T. G. Serum deprivation, but not inhibition of growth per se, induces a hypermutable state in Chinese hamster G12 cells. *Cancer Res.* 1996, 56, 752–756. [PubMed]

87. Bindra, R. S.; Glazer, P. M. Genetic instability and the tumor microenvironment: Towards the concept of microenvironment-induced mutagenesis. *Mutat. Res. Fundam. Mol. Mech. Mutagenesis* 2005, 569, 75–85. [CrossRef] [PubMed]

88. Yuan, J.; Glazer, P. M. Mutagenesis induced by the tumor microenvironment. *Mutat. Res. Fundam. Mol. Mech. Mutagenesis* 1998, 400, 439–446. [CrossRef]

89. Bakhroum, S. F.; Kabeché, L.; Murnane, J. P.; Zaki, B. I.; Compton, D. A. DNA-damage response during mitosis induces whole-chromosome missegregation. *Cancer Discov.* 2014, 4, 1281–1289. [CrossRef] [PubMed]

90. Gentric, G.; Mailet, V.; Paradis, V.; Couton, D.; L’Hermitte, A.; Panasyuk, G.; Fromenty, B.; Celton-Morizur, S.; Desdouets, C.; Ochs, D. Oxidative stress promotes pathologic polyploidization in nonalcoholic fatty liver disease. *J. Clin. Investig.* 2015, 125, 981–992. [CrossRef] [PubMed]

91. Tan, Z.; Chan, Y. J. A.; Chua, Y. J. K.; Rutledge, S. D.; Pavelka, N.; Cimini, D.; Rancati, G. Environmental stresses induce karyotypic instability in colorectal cancer cells. *Mol. Biol. Cell* 2019, 30, 42–55. [CrossRef]

92. Shacter, E.; Weitzman, S. A. Chronic inflammation and cancer. *Oncology* 2002, 16, 217–226. [PubMed]

93. Galipeau, P. C.; Cowan, D. S.; Sanchez, C. A.; Barrett, M. T.; Emond, M. J.; Levine, D. S.; Rabinovitch, P. S.; Reid, B. J. 17p (p53) allelic losses, 4N (G2/tetraploid) populations, and progression to aneuploidy in Barrett’s esophagus. *Proc. Natl. Acad. Sci. USA* 1996, 93, 7081–7084. [CrossRef]

94. Lothschütz, D.; Jennewein, M.; Pahl, S.; Lausberg, H.; Eichler, A.; Mutschler, W.; Hanselmann, R.; Oberringer, M. Polyploidization and centrosome hyperamplification in inflammatory bronchi. *Inflamm. Res.* 2002, 51, 416–422. [CrossRef]

95. Habermann, J.; Lenander, C.; Roblick, U.; Krüger, S.; Ludwig, D.; Alaiya, A.; Freitag, S.; Dümichen, L.; Bruch, H.-P.; Stange, E. Ulcerative Colitis and Colorectal Carcinoma: DNA-Profile, Laminin-5? 2 Chain and Cyclin A Expression as Early Markers for Risk Assessment. *Scand. J. Gastroenterol.* 2001, 36, 751–758. [CrossRef] [PubMed]

96. Slaon, E. M.; Loeliger, K.; Paffen, L.; Poon, A.; Calado, R.; Feng, X.; Padilla-Nash, H.; Chen, J.; Young, N. S. Does a Chronic Inflammatory Process Underlie Clonal Progression In Aplastic Anemia?—In Vitro and In Vivo Evidence That Inflammation Produces Aneuploidy for Chromosomes 7 and 8 In Replicating Cells; American Society of Hematology: Washington, DC, USA, 2010.
97. Cianfarani, S.; Tedeschi, B.; Germani, D.; Prete, S.; Rossi, P.; Vernole, P.; Caporossi, D.; Boscherini, B. In vitro effects of growth hormone (GH) and insulin-like growth factor I and II (IGF-I and-II) on chromosome fragility and p53 protein expression in human lymphocytes. *Eur. J. Clin. Investig.* 1998, 28, 41–47. [CrossRef]

98. Johansson, C.B.; Voussef, S.; Kolecark, K.; Holbrook, C.; Doyonnas, R.; Corbel, S.Y.; Steinman, L.; Rossi, F.M.; Blau, H.M. Extensive fusion of haematopoietic cells with Purkinje neurons in response to chronic inflammation. *Nat. Cell Biol.* 2008, 10, 575–583. [CrossRef]

99. Rosin, M.P.; Anwar, W.A.; Ward, A.J. Inflammation, chromosomal instability, and cancer: The schistosomiasis model. *Cancer Res.* 1994, 54, 1929s–1933s. [PubMed]

100. Matsumoto, Y.; Marusawa, H.; Kinoshita, K.; Niwa, Y.; Sakai, Y.; Chiba, T. Up-regulation of activation-induced cytidine deaminase causes genetic aberrations at the CDKN2b–CDKN2a in gastric cancer. *Gastroenterology* 2010, 139, 1984–1994. [CrossRef] [PubMed]

101. Colotta, F.; Allavena, P.; Sica, A.; Garlanda, C.; Mantovani, A. Cancer-related inflammation, the seventh hallmark of cancer: Links to genetic instability. *Carcinogenesis* 2009, 30, 1073–1081. [CrossRef] [PubMed]

102. Golubkov, V.S.; Boyd, S.; Savinov, A.Y.; Chekanov, A.V.; Osterman, A.L.; Remacle, A.; Rozanov, D.V.; Doxsey, S.J.; Strongin, A.Y. Membrane type-1 matrix metalloproteinase (MT1-MMP) exhibits an important intracellular cleavage function and causes chromosome instability. *J. Biol. Chem.* 2005, 280, 25079–25086. [CrossRef] [PubMed]

103. Sterrnlicht, M.D.; Lochter, A.; Sympson, C.J.; Huey, B.; Rougier, J.P.; Gray, J.W.; Pinkel, D.; Bissell, M.J.; Werb, Z. The stromal proteinase MMP3/stromelysin-1 promotes mammary carcinogenesis. *Cell* 1999, 98, 137–146. [CrossRef]

104. Lochter, A.; Srebrow, A.; Sympson, C.J.; Terracio, N.; Werb, Z.; Bissell, M.J. Misregulation of stromelysin-1 expression in mouse mammary tumor cells accompanies acquisition of stromelysin-1-dependent invasive properties. *J. Biol. Chem.* 1997, 272, 5007–5015. [CrossRef] [PubMed]

105. Suarez-Carmona, M.; Lesage, J.; Cataldo, D.; Gilles, C. EMT and inflammation: Inseparable actors of cancer progression. *Oncol. Rep.* 2017, 805–823. [CrossRef]

106. Comaills, V.; Kabeach, L.; Morris, R.; Buissen, R.; Yu, M.; Madden, M.W.; LiCausi, J.A.; Boukhali, M.; Tajima, K.; Pan, S. Genomic instability is induced by persistent proliferation of cells undergoing epithelial-to-mesenchymal transition. *Cell Rep.* 2016, 17, 2632–2647. [CrossRef] [PubMed]

107. Alfadda, A.A.; Sallam, R.M. Reactive oxygen species in health and disease. *J. Biomed. Biotechnol.* 2012, 142, w13659. [CrossRef] [PubMed]

108. Chiera, F.; Meccia, E.; Degani, G.; Aquilina, G.; Pietraforte, D.; Minetti, M.; Lambeth, D.; Bignami, M. Overexpression of human NOX1 complex induces genome instability in mammalian cells. *Free Radic. Biol. Med.* 2008, 44, 332–342. [CrossRef]

109. Limoli, C.L.; Giedzinski, E. Induction of chromosomal instability by chronic oxidative stress. *Neoplasia* 2003, 5, 339–346. [CrossRef]

110. Limoli, C.L.; Giedzinski, E.; Morgan, W.F.; Swarts, S.G.; Jones, G.D.; Hyun, W. Persistent oxidative stress in chromosomally unstable cells. *Cancer Res.* 2003, 63, 3107–3111.

111. Samper, E.; Nicholls, D.; Melov, S. Mitochondrial oxidative stress causes chromosomal instability of mouse embryonic fibroblasts. *Aging Cell* 2003, 2, 277–285. [CrossRef]

112. Mishra, P.K.; Raghuram, G.V.; Panwar, H.; Jain, D.; Pandey, H.; Maudar, K.K. Mitochondrial oxidative stress elicits chromosomal instability after exposure to isocyanates in human kidney epithelial cells. *Free Radic. Res.* 2009, 43, 718–728. [CrossRef]

113. Houben, J.M.; Moonen, H.J.; van Schooten, F.J.; Hageman, G.J. Telomere length assessment: Biomarker of chronic oxidative stress? *Free Radic. Biol. Med.* 2008, 44, 235–246. [CrossRef]

114. Chow, J.P.; Poon, R.Y. DNA damage and polyploidyization. In *Polyploidyization and Cancer*; Springer: Berlin/Heidelberg, Germany, 2010; pp. 57–71.

115. Ivanov, A.; Cragg, M.S.; Erenpreisa, J.; Emzinsh, D.; Lukman, H.; Illidge, T.M. Endopolyploid cells produced after severe genotoxic damage have the potential to repair DNA double strand breaks. *J. Cell Sci.* 2003, 116, 4095–4106. [CrossRef] [PubMed]

116. Andreassen, P.R.; Lacroix, F.B.; Lohez, O.D.; Margolis, R.L. Neither p21WAF1 nor 14-3-3σ prevents G2 progression to mitotic catastrophe in human colon carcinoma cells after DNA damage, but p21WAF1 induces stable G1 arrest in resulting tetraploid cells. *Cancer Res.* 2001, 61, 7660–7668. [CrossRef]

117. Tan, Z.; Chan, Y.J.A.; Ly, Y.E.; Rancati, G. Mammalian cells undergo endoreduplication in response to lactic acidosis. *Sci. Rep.* 2018, 8, 1–10. [CrossRef]

118. Machida, K.; Liu, J.-C.; McNamara, G.; Levine, A.; Duan, L.; Lai, M.M. Hepatitis C virus causes uncoupling of mitotic checkpoint and chromosomal polyploidy through the Rb pathway. *J. Virol.* 2009, 83, 12590–12600. [CrossRef]

119. Bloomfield, M.; Duesberg, P. Karyotype alteration generates the neoplastic phenotypes of SV40-infected human and rodent cells. *Mol. Cytogenet.* 2015, 8, 79. [CrossRef]

120. McCormack, A.; Fan, J.L.; Duesberg, M.; Bloomfield, M.; Fiala, C.; Duesberg, P. Individual karyotypes at the origins of cervical carcinomas. *Mol. Cytogenet.* 2013, 6, 44. [CrossRef] [PubMed]

121. Bloomfield, M.; McCormack, A.; Mandrioli, D.; Fiala, C.; Aldaz, C.M.; Duesberg, P. Karyotypic evolutions of cancer species in rats during the long latent periods after injection of nitrosourea. *Mol. Cytogenet.* 2014, 7, 71. [CrossRef] [PubMed]

122. Cortez, B.A.; Teixeira, P.R.; Redick, S.; Doxsey, S.; Machado-Santelli, G.M. Multipolar mitosis and aneuploidy after chyrosistle treatment: A consequence of abscission failure and cytokinesis regression. *Oncotarget* 2016, 7, 8979. [CrossRef] [PubMed]

123. Scheffner, M.; Werness, B.A.; Huibregtse, J.M.; Levine, A.J.; Howley, P.M. The E6 oncprotein encoded by human papillomavirus types 16 and 18 promotes the degradation of p53. *Cell* 1990, 63, 1129–1136. [CrossRef]
124. Brechot, C.; Pourcel, C.; Louise, A.; Rain, B.; Tiollais, P. Presence of integrated hepatitis B virus DNA sequences in cellular DNA of human hepatocellular carcinoma. *Nature* 1980, 286, 533–535. [CrossRef]

125. Perera, F.; Lin, C.-j.; Lu, T.; Tang, D. Shorter telomere length in cord blood associated with prenatal air pollution exposure: Benefits of intervention. *Environ. Int.* 2018, 113, 335–340. [CrossRef]

126. Awada, Z.; Sleiman, F.; Maitlacak, A.; Mouneime, Y.; Tamim, H.; Zgheib, N. BPA exposure is associated with non-monotonic alteration in ESR1 promoter methylation in peripheral blood of men and shorter relative telomere length in peripheral blood of women. *J. Exp. Sci. Environ. Epidemiol.* 2019, 118, 128. [CrossRef] [PubMed]

127. Zota, A.R.; Needham, B.L.; Blackburn, E.H.; Lin, J.; Park, S.K.; Rehkopf, D.H.; Epel, E.S. Associations of cadmium and lead exposure with leukocyte telomere length: Findings from National Health and Nutrition Examination Survey, 1999–2002. *Am. J. Epidemiol.* 2015, 181, 127–136. [CrossRef]

128. Maser, R.S.; DePinho, R.A. Connecting chromosomes, crisis, and cancer. *Science* 2002, 297, 565–569. [CrossRef] [PubMed]

129. Davoli, T.; Denchi, E.L.; de Lange, T. Persistent telomere damage induces bypass of mitosis and tetraploidy. *Cell* 2010, 141, 81–93. [CrossRef] [PubMed]

130. Knouse, K.A.; Lopez, K.E.; Bachofner, M.; Amon, A. Chromosome segregation fidelity in epithelia requires tissue architecture. *Cell* 2018, 175, 200–211.e213. [CrossRef] [PubMed]

131. Oberringer, M.; Lothschütz, D.; Jennewein, M.; Koschnick, M.; Mutschler, W.; Hanselmann, R.G. Centrosome multiplication accompanies a transient clustering of polyplloid cells during tissue repair. *Mol. Cell Biol. Res. Commun.* 1999, 2, 190–196. [CrossRef]

132. Lewis, J.M.; Truong, T.N.; Schwartz, M.A. Integrins regulate the apoptotic response to DNA damage through modulation of p53. *Proc. Natl. Acad. Sci. USA* 2002, 99, 3627–3632. [CrossRef]

133. Truong, T.; Sun, G.; Doorly, M.; Wang, J.; Schwartz, M.A. Modulation of DNA damage-induced apoptosis by cell adhesion is independently mediated by p53 and c-Abl. *Proc. Natl. Acad. Sci. USA* 2003, 100, 10281–10286. [CrossRef]

134. Knouse, K.A.; Wu, J.; Whittaker, C.A.; Amon, A. Single cell sequencing reveals low levels of aneuploidy across mammalian cell lines. *Cell Cycle* 2016, 15, 274–282. [CrossRef] [PubMed]

135. Andreassen, PR.; Lohez, O.D.; Lacroix, F.B.; Margolis, R.L. Tetraploid state induces p53-dependent arrest of nontransformed mammalian cells in G1. *Mol. Biol. Cell* 2001, 12, 1315–1328. [CrossRef]

136. Newell, G.; Spitz, M.; Sider, J. Cancer and age. In Proceedings of Seminars in Oncology. Unpublished work.

137. Rubin, H. Cancer as a dynamic developmental disorder. *Cancer Res.* 1985, 45, 2935–2942. [PubMed]

138. Rehen, S.K.; McConnell, M.J.; Kaushal, D.; Kingsbury, M.A.; Yang, A.H.; Chun, J. Chromosomal variation in neurons of the developing and adult mammalian nervous system. *Proc. Natl. Acad. Sci. USA* 2001, 98, 13361–13366. [CrossRef]

139. Baker, D.J.; Dawlaty, M.M.; Wijskate, T.; Jeganathan, K.B.; Malureanu, L.; Van Ree, J.H.; Crespo-Diaz, R.; Reyes, S.; Seaburg, L.; Shapiro, V. Increased expression of BubR1 protects against aneuploidy and cancer and extends healthy lifespan. *Nat. Cell Biol.* 2010, 188, 369–381. [CrossRef] [PubMed]

140. Brechot, C.; Pourcel, C.; Louise, A.; Rain, B.; Tiollais, P. Presence of integrated hepatitis B virus DNA sequences in cellular DNA of human hepatocellular carcinoma. *Nature* 1980, 286, 533–535. [CrossRef]

141. Perera, F.; Lin, C.-j.; Lu, T.; Tang, D. Shorter telomere length in cord blood associated with prenatal air pollution exposure: Benefits of intervention. *Environ. Int.* 2018, 113, 335–340. [CrossRef]

142. Awada, Z.; Sleiman, F.; Mailhac, A.; Mouneime, Y.; Tamim, H.; Zgheib, N. BPA exposure is associated with non-monotonic alteration in ESR1 promoter methylation in peripheral blood of men and shorter relative telomere length in peripheral blood of women. *J. Exp. Sci. Environ. Epidemiol.* 2019, 118, 128. [CrossRef] [PubMed]

143. Jonkers, J.; Derksen, P.W. Modeling metastatic breast cancer in mice. *J. Mammary Gland Biol. Neoplasia* 2007, 12, 191–203. [CrossRef]

144. Franklin, O.S.; Chin, J.L.; Engleand, L.S.; Greco, W.R.; Pontes, J.E.; Rustum, Y.M. Relationship between DNA ploidy, glandular differentiation, and tumor spread in human prostate cancer. *Cancer Res.* 1985, 45, 1418–1423. [PubMed]

145. Korabiowska, M.; Brinck, U.; Kotthaus, I.; Berger, H.; Droese, M. Analysis of the DNA content in the progression of recurrent and metastatic melanomas. *Anticancer Res.* 2000, 20, 2791–2794. [PubMed]
153. Laubert, T.; Bente, V.; Freitag-Wolf, S.; Voulgaris, H.; Oberländer, M.; Schillo, K.; Kleemann, M.; Bürc, K.; Bruch, H.-P.; Roblick, U.J. Aneuploidy and elevated CEA indicate an increased risk for metachronous metastasis in colorectal cancer. *Int. J. Colorectal Dis.* 2013, 28, 767–775. [CrossRef]

154. Li, L.; Mu, K.; Zhou, G.; Lan, L.; Auer, G.; Zetterberg, A. Genomic instability and proliferative activity as risk factors for distant metastases in breast cancer. *Br. J. Cancer* 2008, 99, 513–519. [CrossRef] [PubMed]

155. Turajlic, S.; Xu, H.; Litchfield, K.; Rowan, A.; Chambers, T.; Lopez, J.I.; Nicol, D.; O’Brien, T.; Larkin, J.; Horswell, S. Tracking cancer evolution reveals constrained routes to metastases: TRACERx renal. *Cell* 2018, 173, 581–594.e512. [CrossRef]

156. Bakhoum, S.F.; Ngo, B.; Laughney, A.M.; Cavallo, J.A.; Murphy, C.J.; Ly, P.; Shah, P.; Sriman, R.K.; Watkins, T.B.K.; Taunk, N.K.; et al. Chromosomal instability drives metastasis through a cytosolic DNA response. *Nature* 2018, 553, 467–472. [CrossRef]

157. Tijhuis, A.E.; Johnson, S.C.; McClelland, S.E. The emerging links between chromosomal instability (CIN), metastasis, inflammation and tumour immunity. *Mol. Cytogenet.* 2019, 12, 17. [CrossRef] [PubMed]

158. Fallenius, A.G.; Auer, G.U.; Carstensen, J.M. Prognostic significance of DNA measurements in 409 consecutive breast cancer patients. *Cancer* 1988, 62, 331–341. [CrossRef] [PubMed]

159. Fallenius, A.G.; Auer, G.U.; Franzén, S.A. Predictive value of nuclear DNA content in breast cancer in relation to clinical and morphologic factors. A retrospective study of 227 consecutive cases. *Cancer* 1988, 62, 521–530. [CrossRef]

160. Sheffer, M.; Bacolod, M.D.; Zuck, O.; Giardina, S.F.; Pincas, H.; Barany, F.; Bruch, H.-P.; Notterman, D.A.; Domany, E. Association of survival and disease progression with chromosomal instability: A genomic exploration of colorectal cancer. *Proc. Natl. Acad. Sci. USA* 2009, 106, 7131–7136. [CrossRef]

161. Walther, A.; Houlston, R.; Tomlinson, I. Association between chromosomal instability and prognosis in colorectal cancer: A meta-analysis. *Gut* 2008, 57, 941–950. [CrossRef] [PubMed]

162. Carter, S.L.; Eklund, A.C.; Kohane, I.S.; Harris, L.N.; Szallasi, Z. A signature of chromosomal instability inferred from gene expression profiles predicts clinical outcome in multiple human cancers. *Nat. Genet.* 2006, 38, 1043. [CrossRef] [PubMed]

163. Silk, A.D.; Tasadil, L.M.; Hollnad, A.J.; Vitre, B.; Cleveland, D.W.; Weaver, B.A. Chromosome missegregation rate predicts whether aneuploidy will promote or suppress tumors. *Proc. Natl. Acad. Sci. USA* 2013, 110, E4134–E4141. [CrossRef]

164. Bolhaqueiro, A.C.; Ponsioen, B.; Bakker, B.; Klaasen, S.J.; Kucukkose, E.; van Jaarsveld, R.H.; Vivi, J.; Verlaan-Klink, I.; Hami, N.; Spierings, D.C. Ongoing chromosomal instability and karyotype evolution in human colorectal cancer organoids. *Nat. Genet.* 2019, 51, 824–834. [CrossRef]

165. Nicholson, J.M.; Cimini, D. Link between aneuploidy and chromosome instability. In *International Review of Cell and Molecular Biology*; Elsevier: Amsterdam, The Netherlands, 2015; Volume 315, pp. 299–317.

166. Nicholson, J.M.; Cimini, D. Cancer karyotypes: Survival of the fittest. *Front. Oncol.* 2013, 3, 148. [CrossRef]

167. Thompson, S.L.; Compton, D.A. Examining the link between chromosomal instability and aneuploidy in human cells. *J. Cell Biol.* 2008, 180, 665–672. [CrossRef]

168. Valind, A.; Jin, Y.; Gisselsson, D. Elevated tolerance to aneuploidy in cancer cells: Estimating the fitness effects of chromosome number alterations by in silico modelling of somatic genome evolution. *PLoS ONE* 2013, 8, e70445. [CrossRef]

169. Bloomfield, M.; Duesberg, P. Inherent variability of cancer-specific aneuploidy generates metastases. *Mol. Cytogenet.* 2016, 9, 90. [CrossRef]

170. Tasadil, L.M.; Britigan, E.M.; Weaver, B.A. 2n or not 2n: Aneuploidy, polyploidy and chromosomal instability in primary and tumor cells. *Semin. Cell Dev. Biol.* 2013, 24, 370–379. [CrossRef] [PubMed]

171. Kuznetsova, A.Y.; Seget, K.; Moeller, G.K.; de Pagter, M.S.; de Roos, J.A.; Dürrbaum, M.; Kuffer, C.; Müller, S.; Zaman, G.J.; Kloosterman, W.P. Chromosomal instability, tolerance of mitotic errors and multidrug resistance are promoted by tetraploidization of tumor cells. *Semin. Cell Dev. Biol.* 2011, 22, 370–379. [CrossRef] [PubMed]

172. Ganem, N.J.; Storchova, Z.; Faucett, C. The consequences of tetraploidy and aneuploidy. *Cell Rep.* 2014, 15, 175–185. [CrossRef]

173. Ly, P.; Eskioğlu, U.; Kim, S.B.; Roig, A.I.; Hight, S.K.; Lulla, D.R.; Zou, Y.S.; Batten, K.; Wright, W.E.; Shay, J.W. Characterization of aneuploid populations with trisomy 7 and 20 derived from diploid human colon epithelial cells. *Neoplasia* 2011, 13, 348. [CrossRef]

174. Duncan, A.W.; Newell, A.E.H.; Bi, W.; Finegold, M.J.; Olson, S.B.; Beaudet, A.L.; Grompe, M. Aneuploidy as a mechanism for stress-induced liver adaptation. *J. Clin. Investig.* 2012, 122, 3307–3315. [CrossRef]

175. Rutledge, S.D.; Douglas, T.A.; Nicholson, J.M.; Vila-Casadesús, M.; Kanzler, C.L.; Wangsa, D.; Barroso-Vilares, M.; Kale, S.D.; Logarinho, E.; Cimini, D. Selective advantage of trisomic human cells cultured in non-standard conditions. *Sci. Rep.* 2016, 6, 22828. [CrossRef]

176. Sheltzer, J.M.; Ko, J.H.; Replogle, J.M.; Burgos, N.C.H.; Chung, E.S.; Meehl, C.M.; Sayles, N.M.; Passerini, V.; Storchova, Z.; Amon, A. Single-chromosome gains commonly function as tumor suppressors. *Cancer Cell* 2017, 31, 240–255. [CrossRef]
180. Williams, B.R.; Prabhu, V.R.; Hunter, K.E.; Glazier, C.M.; Whittaker, C.A.; Housman, D.E.; Amon, A. Aneuploidy affects proliferation and spontaneous immortalization in mammalian cells. Science 2008, 322, 703–709. [CrossRef] [PubMed]

181. He, Q.; Au, B.; Kulkarni, M.; Shen, Y.; Lim, K.J.; Maimaiti, J.; Wong, C.K.; Luijten, M.N.; Chong, H.C.; Lim, E.H. Chromosomal instability-induced senescence potentiates cell non-autonomous tumourigenic effects. Oncogenesis 2018, 7, 62. [CrossRef] [PubMed]

182. Andriani, G.A.; Almeida, V.P.; Faggioli, F.; Mauro, M.; Tsai, W.L.; Santambrogio, L.; Maslov, A.; Gadina, M.; Campisi, J.; Viji, G. Whole Chromosome Instability induces senescence and promotes SASP. Sci. Rep. 2016, 6, 35218. [CrossRef]

183. Elizalde, S.; Laughnhey, A.M.; Bakhoun, S.F. A Markov chain for numerical chromosomal instability in clonally expanding populations. PLoS Comput. Biol. 2018, 14, e1006447. [CrossRef]

184. Habermann, J.K.; Doering, J.; Hautaniemi, S.; Roblick, U.J.; Bündgen, N.K.; Nicorici, D.; Kronenwett, U.; Rathnagiriswaran, S.; Mettu, R.K.; Ma, Y. The gene expression signature of genomic instability in breast cancer is an independent predictor of clinical outcome. Int. J. Cancer 2009, 124, 1552–1564. [CrossRef]

185. Kronenwett, U.; Ploner, A.; Zetterberg, A.; Bergh, J.; Hall, P.; Auer, G.; Pawitan, Y. Genomic instability and prognosis in breast carcinomas. Cancer Epidemiol. Prev. Biomark. 2006, 15, 1630–1635. [CrossRef] [PubMed]

186. Jamal-Hanjani, M.; A'hern, R.; Birkbak, N.; Gorman, P.; Grönroos, E.; Ngang, S.; Nicola, P.; Rahman, L.; Thanopoulou, E.; Kelly, G. Extreme chromosomal instability forecasts improved outcome in ER-negative breast cancer: A prospective validation cohort study from the TACT trial. Ann. Oncol. 2015, 26, 1340–1346. [CrossRef] [PubMed]

187. Roylance, R.; Endesfelder, D.; Gorman, P.; Burrell, R.A.; Sander, J.; Tomlinson, I.; Hanby, A.M.; Speirs, V.; Richardson, A.L.; Birkbak, N.J. Relationship of extreme chromosomal instability with long-term survival in a retrospective analysis of primary breast cancer. Cancer Epidemiol. Prev. Biomark. 2011, 20, 2183–2194. [CrossRef] [PubMed]

188. Birkbak, N.J.; Eklund, A.C.; Li, Q.; McClelland, S.E.; Endesfelder, D.; Tan, P.; Tan, I.B.; Richardson, A.L.; Szallasi, Z.; Swanton, C. Paradoxical relationship between chromosomal instability and survival outcome in cancer. Cancer Res. 2011, 71, 3447–3452. [CrossRef]

189. Elizalde, S.; Laughney, A.M.; Bakhoum, S.F. A Markov chain for numerical chromosomal instability in clonally expanding populations. PLoS Comput. Biol. 2014, 10, e1004476. [CrossRef] [PubMed]

190. Janssen, A.; Kops, G.J.; Medema, R.H. E elevating the frequency of chromosome mis-segregation as a strategy to kill tumor cells. Proc. Natl. Acad. Sci. USA 2009, 106, 19108–19113. [CrossRef] [PubMed]

191. Lukow, D.A.; Sausville, E.L.; Suri, P.; Chunduri, N.K.; Leu, J.; Kendall, J.; Wang, Z.; Storchova, Z.; Sheltzer, J.M.; Pawitan, Y. Genomic instability and prognosis in breast carcinomas. Cancer Epidemiol. Prev. Biomark. 2006, 15, 1630–1635. [CrossRef] [PubMed]

192. Ibrahim-Hashim, A.; Gillies, R.J.; Brown, J.S.; Gatenby, R.A. Coevolution of tumor cells and their microenvironment: “niche construction.” In Ecology and Evolution of Cancer; Elsevier: Amsterdam, The Netherlands, 2017; pp. 111–117.

193. Han, X.; Hui, C. Niche construction on environmental gradients: The formation of fitness valley and stratified genotypic distributions. PLoS ONE 2014, 9, e99775. [CrossRef]

194. Matthews, B.; De Meester, L.; Jones, C.G.; Ibelings, B.W.; Bouma, T.J.; Nuutinen, V.; Van De Koppel, J.; Odling-Smee, J. Under niche construction: An operational bridge between ecology, evolution, and ecosystem science. Ecol. Monogr. 2014, 84, 245–263. [CrossRef]

195. Bergman, A.; Gligorijevic, B. Niche construction game cancer cells play. Eur. Phys. J. Plus 2015, 130, 203. [CrossRef]

196. Day, R.L.; Laland, K.N.; Odling-Smej, F.J. Rethinking adaptation: The niche-construction perspective. Perspect. Biol. Med. 2003, 46, 80–95. [CrossRef] [PubMed]

197. Ibrahim-Hashim, A.; Gillies, R.J.; Brown, J.S.; Gatenby, R.A. Coevolution of tumor cells and their microenvironment: “niche construction in cancer”. In Ecology and Evolution of Cancer; Elsevier: Amsterdam, The Netherlands, 2017; pp. 111–117.

198. Han, X.; Hui, C. Niche construction on environmental gradients: The formation of fitness valley and stratified genotypic distributions. PLoS ONE 2014, 9, e99775. [CrossRef]

199. Matthews, B.; De Meester, L.; Jones, C.G.; Ibelings, B.W.; Bouma, T.J.; Nuutinen, V.; Van De Koppel, J.; Odling-Smej, F.J. Under niche construction: An operational bridge between ecology, evolution, and ecosystem science. Ecol. Monogr. 2014, 84, 245–263. [CrossRef]

200. Day, R.L.; Laland, K.N.; Odling-Smej, F.J. Rethinking adaptation: The niche-construction perspective. Perspect. Biol. Med. 2003, 46, 80–95. [CrossRef] [PubMed]

201. Ibrahim-Hashim, A.; Gillies, R.J.; Brown, J.S.; Gatenby, R.A. Coevolution of tumor cells and their microenvironment: “niche construction in cancer”. In Ecology and Evolution of Cancer; Elsevier: Amsterdam, The Netherlands, 2017; pp. 111–117.

202. Han, X.; Hui, C. Niche construction on environmental gradients: The formation of fitness valley and stratified genotypic distributions. PLoS ONE 2014, 9, e99775. [CrossRef]

203. Matthews, B.; De Meester, L.; Jones, C.G.; Ibelings, B.W.; Bouma, T.J.; Nuutinen, V.; Van De Koppel, J.; Odling-Smej, F.J. Under niche construction: An operational bridge between ecology, evolution, and ecosystem science. Ecol. Monogr. 2014, 84, 245–263. [CrossRef]

204. Zhu, J.; Tsai, H.-J.; Gordon, M.R.; Li, R. Cellular stress associated with aneuploidy. Dev. Cell 2018, 44, 420–431. [CrossRef] [PubMed]

205. Weinberg, R.A. Coevolution in the tumor microenvironment. Nat. Genet. 2008, 40, 494. [CrossRef] [PubMed]

206. Donnelly, N.; Passerini, V.; Durrbaum, M.; Stinglee, S.; Storchova, Z. HSF1 deficiency and impaired HSP90-dependent protein folding are hallmarks of aneuploid human cells. EMBO J. 2014, 33, 2374–2387. [CrossRef] [PubMed]

207. Donnelly, N.; Storchova, Z. Aneuploidy and proteotoxic stress in cancer. Mol. Cell Oncol. 2015, 2, e976491. [CrossRef] [PubMed]
208. Oromendia, A.B.; Dodgson, S.E.; Amon, A. Aneuploidy causes proteotoxic stress in yeast. *Genes Dev.* 2012, 26, 2696–2708. [CrossRef]

209. Cubillos-Ruiz, J.R.; Silberman, P.C.; Rutkowski, M.R.; Chopra, S.; Perales-Puchalt, A.; Song, M.; Zhang, S.; Bettigole, S.E.; Gupta, D.; Holcomb, K. ER stress sensor XBP1 controls anti-tumor immunity by disrupting dendritic cell homeostasis. *Cell* 2015, 161, 1527–1538. [CrossRef]

210. Mahadevan, N.R.; Rodvold, J.; Sepulveda, H.; Rossi, S.; Drew, A.F.; Zanetti, M. Transmission of endoplasmic reticulum stress and pro-inflammation from tumor cells to myeloid cells. *Proc. Natl. Acad. Sci. USA* 2011, 108, 6561–6566. [CrossRef] [PubMed]

211. Mahadevan, N.R.; Anufreichik, V.; Rodvold, J.J.; Chiu, K.T.; Sepulveda, H.; Zanetti, M. Cell-extrinsic effects of tumor ER stress imprint myeloid dendritic cells and impair CD8+ T cell priming. *PLoS ONE* 2012, 7, e51845. [CrossRef]

212. Xian, S.; Searles, S.; Sahani, P.; Waller, T.C.; Jepsen, K.; Carter, H.; Zanetti, M. The unfolded protein response links tumor aneuploidy to local immune dysregulation. *bioRxiv* 2020. [CrossRef]

213. Newman, D.L.; Gregory, S.L. Co-operation between aneuploidy and metabolic changes in driving tumorigenesis. *Int. J. Mol. Sci.* 2019, 20, 4611. [CrossRef] [PubMed]

214. Li, M.; Fang, X.; Baker, D.J.; Guo, L.; Gao, X.; Wei, Z.; Han, S.; Van Deursen, J.M.; Zhang, P. The ATM–p53 pathway suppresses aneuploidy-induced tumorigenesis. *Proc. Natl. Acad. Sci. USA* 2010, 107, 14188–14193. [CrossRef]

215. Stingele, S.; Steohr, G.; Peplowska, K.; Cox, J.; Mann, M.; Storchova, Z. Global analysis of genome, transcriptome and proteome reveals the response to aneuploidy in human cells. *Mol. Syst. Biol.* 2012, 8, 608. [CrossRef] [PubMed]

216. Tang, Y.-C.; Yuwen, H.; Wang, K.; Bruno, P.M.; Bullock, K.; Deik, A.; Santaguida, S.; Trakala, M.; Pfau, S.J.; Zhong, N. Aneuploid cell survival relies upon sphingolipid homeostasis. *Cancer Res.* 2017, 77, 5272–5286. [CrossRef]

217. Biczowa, B.; Kieler, J.; Moore, J. Comparative studies of a near-tetraploid and a near-diploid line of Ehrlich’s ascites tumor physiology and cell division in haploid yeast. *Eur. J. Cancer (1965)* 2013, 49, 1378–1388. [CrossRef]

218. Beaty, B.T.; Wang, Y.; Bravo-Cordero, J.J.; Sharma, V.P.; Miskolci, V.; Hodgson, L.; Condeelis, J. Talin regulates moesin-NHE-1 recruitment to invadopodia and promotes mammary tumor metastasis. *J. Cell Biol.* 2014, 205, 737–751. [CrossRef] [PubMed]

219. Estrella, V.; Chen, T.; Lloyd, M.; Wojtkowiak, J.; Cornnell, H.H.; Ibrahim-Hashim, A.; Bailey, K.; Balaguranathan, Y.; Rothenberg, J.M.; Sloane, B.F.; et al. Acidity generated by the tumor microenvironment drives local invasion. *Cancer Res.* 2013, 73, 1524–1535. [CrossRef]

220. Huber, V.; Camisaschi, C.; Berzi, A.; Ferro, S.; Lugini, L.; Triulzi, T.; Tuccitto, A.; Tagliabue, E.; Castelli, C.; Rivoltini, L. Cancer acidity: An ultimate frontier of tumor immune escape and a novel target of immunomodulation. *Semin Cancer Biol.* 2017, 43, 74–89. [CrossRef] [PubMed]

221. Sullivan, M.R.; Danai, L.V.; Lewis, C.A.; Chan, S.H.; Gui, D.Y.; Kunchok, T.; Dennstedt, E.A.; Vander Heiden, M.G.; Muir, A. Quantification of microenvironmental metabolites in murine cancers reveals determinants of tumor nutrient availability. *Elife* 2019, 8, e44235. [CrossRef] [PubMed]

222. Zhang, J.; Wang, Y.; Zhou, Y.; He, Q.-Y. Jolkinolide B induces apoptosis of colorectal carcinoma through ROS-ER stress-Ca2+-mitochondria dependent pathway. *Oncotarget* 2017, 8, 9123. [CrossRef]

223. Newman, D.L.; Thurgood, L.A.; Gregory, S.L. The impact of aneuploidy on cellular homeostasis. *Free Radic. Res.* 2019, 53, 705–713. [CrossRef]

224. Dephoure, N.; Hwang, S.; O’Sullivan, C.; Dodgson, S.E.; Gygi, S.P.; Amon, A.; Torres, E.M. Quantitative proteomic analysis reveals posttranslational responses to aneuploidy. *Elife* 2014, 3, e03023. [CrossRef] [PubMed]

225. Sheltzer, J.M. A transcriptional and metabolic signature of primary aneuploidy is present in chromosomally unstable cancer cells and informs clinical prognosis. *Cancer Res.* 2013, 73, 6401–6412. [CrossRef]

226. Cubillos-Ruiz, J.R.; Silberman, P.C.; Rutkowski, M.R.; Chopra, S.; Perales-Puchalt, A.; Song, M.; Zhang, S.; Bettigole, S.E.; Gupta, D.; Holcomb, K. ER stress sensor XBP1 controls anti-tumor immunity by disrupting dendritic cell homeostasis. *Cell* 2015, 161, 1527–1538. [CrossRef]

227. Sheltzer, J.M. A transcriptional and metabolic signature of primary aneuploidy is present in chromosomally unstable cancer cells and informs clinical prognosis. *Cancer Res.* 2013, 73, 6401–6412. [CrossRef]

228. Sheltzer, J.M. A transcriptional and metabolic signature of primary aneuploidy is present in chromosomally unstable cancer cells and informs clinical prognosis. *Cancer Res.* 2013, 73, 6401–6412. [CrossRef]

229. Sullivan, M.R.; Danai, L.V.; Lewis, C.A.; Chan, S.H.; Gui, D.Y.; Kunchok, T.; Dennstedt, E.A.; Vander Heiden, M.G.; Muir, A. Quantification of microenvironmental metabolites in murine cancers reveals determinants of tumor nutrient availability. *Elife* 2019, 8, e44235. [CrossRef] [PubMed]

230. Zhang, J.; Wang, Y.; Zhou, Y.; He, Q.-Y. Jolkinolide B induces apoptosis of colorectal carcinoma through ROS-ER stress-Ca2+-mitochondria dependent pathway. *Oncotarget* 2017, 8, 9123. [CrossRef]

231. Newman, D.L.; Thurgood, L.A.; Gregory, S.L. The impact of aneuploidy on cellular homeostasis. *Free Radic. Res.* 2019, 53, 705–713. [CrossRef]

232. Dephoure, N.; Hwang, S.; O’Sullivan, C.; Dodgson, S.E.; Gygi, S.P.; Amon, A.; Torres, E.M. Quantitative proteomic analysis reveals posttranslational responses to aneuploidy. *Elife* 2014, 3, e03023. [CrossRef] [PubMed]

233. Shaukat, Z.; Liu, D.; Choo, A.; Hussain, R.; O’Keefe, L.; Richards, R.; Saint, R.; Gregory, S. Chromosomal instability causes sensitivity to metabolic stress. *Oncogene* 2015, 34, 4044–4055. [CrossRef] [PubMed]

234. Weinberg, F.; Ramnath, N.; Nagrah, D. Reactive oxygen species in the tumor microenvironment: An overview. *Cancers* 2019, 11, 1191. [CrossRef]

235. Liao, Z.; Chua, D.; Tan, N.S. Reactive oxygen species: A volatile driver of field cancerization and metastasis. *Mol. Cancer* 2019, 18, 1–10. [CrossRef]

236. Berlett, B.S.; Stadtman, E.R. Protein oxidation in aging, disease, and oxidative stress. *J. Biol. Chem.* 1997, 272, 20313–20316. [CrossRef]

237. Cubillos-Ruiz, J.R.; Silberman, P.C.; Rutkowski, M.R.; Chopra, S.; Perales-Puchalt, A.; Song, M.; Zhang, S.; Bettigole, S.E.; Gupta, D.; Holcomb, K. ER stress sensor XBP1 controls anti-tumor immunity by disrupting dendritic cell homeostasis. *Cell* 2015, 161, 1527–1538. [CrossRef]

238. Cubillos-Ruiz, J.R.; Silberman, P.C.; Rutkowski, M.R.; Chopra, S.; Perales-Puchalt, A.; Song, M.; Zhang, S.; Bettigole, S.E.; Gupta, D.; Holcomb, K. ER stress sensor XBP1 controls anti-tumor immunity by disrupting dendritic cell homeostasis. *Cell* 2015, 161, 1527–1538. [CrossRef]

239. Cubillos-Ruiz, J.R.; Silberman, P.C.; Rutkowski, M.R.; Chopra, S.; Perales-Puchalt, A.; Song, M.; Zhang, S.; Bettigole, S.E.; Gupta, D.; Holcomb, K. ER stress sensor XBP1 controls anti-tumor immunity by disrupting dendritic cell homeostasis. *Cell* 2015, 161, 1527–1538. [CrossRef]
235. Martinez-Outschoorn, U.E.; Balliet, R.M.; Rivadeneira, D.; Chiavarina, B.; Pavlidis, S.; Wang, C.; Whitaker-Menezes, D.; Daumer, K.; Lin, Z.; Witkiewicz, A. Oxidative stress in cancer-associated fibroblasts drives tumor-stroma co-evolution: A new paradigm for understanding tumor metabolism, the field effect and genomic instability in cancer cells. Cell Cycle 2010, 9, 3276–3296. [CrossRef]

236. Reuter, S.; Gupta, S.C.; Chaturvedi, M.M.; Aggarwal, B.B. Oxidative stress, inflammation, and cancer: How are they linked? Free Radic. Biol. Med. 2010, 49, 1603–1616. [CrossRef] [PubMed]

237. Coussens, L.M.; Werb, Z. Inflammation and cancer. Nature 2002, 420, 860–867. [CrossRef]

238. Schoppmann, S.F.; Birner, P.; Stöckl, J.; Kalt, R.; Ullrich, R.; Cauvic, C.; Kriehuber, E.; Nagy, K.; Alitalo, K.; Kerjaschki, D. Tumor-associated macrophages express lymphatic endothelial growth factors and are related to peritumoral lymphangiogenesis. Am. J. Pathol. 2002, 161, 947–956. [CrossRef]

239. Zimmerman, M.A.; Huang, Q.; Li, F.; Liu, X.; Li, C.-Y. Cell death–stimulated cell proliferation: A tissue regeneration mechanism usurped by tumors during radiotherapy. Semin. Radiat. Oncol. 2013, 23, 288–295. [CrossRef] [PubMed]

240. Pérez-Garrio, A.; Steller, H. Spreading the word: Non-autonomous effects of apoptosis during development, regeneration and disease. Development 2015, 142, 3253–3262. [CrossRef] [PubMed]

241. Rock, K.L.; Kono, H. The inflammatory response to cell death. Annu. Rev. Pathol. Mech. Dis. 2008, 3, 99–126. [CrossRef]

242. Yang, Y.; Jiang, G.; Zhang, P.; Fan, J. Programmed cell death and its role in inflammation. Mil. Med. Res. 2015, 2, 12. [CrossRef]

243. Liu, S.; Edgerton, S.M.; Moore, D.H.; Thor, A.D. Measures of cell turnover (proliferation and apoptosis) and their association with survival in breast cancer. Clin. Cancer Res. 2001, 7, 1716–1723. [CrossRef]

244. Soini, Y.; Paäkkö, P.; Lehto, V. Histopathological evaluation of apoptosis in cancer. Am. J. Pathol. 1998, 153, 1041. [CrossRef]

245. Dou, Z.; Ghosh, K.; Vizioli, M.G.; Zhu, J.; Sen, P.; Wangensteen, K.J.; Simithy, J.; Lan, Y.; Lin, Y.; Zhou, Z. Cytoplasmic chromatin triggers inflammation in senescence and cancer. Nature 2017, 550, 402–406. [CrossRef]

246. Campisi, J. Aging, cellular senescence, and cancer. Annu. Rev. Physiol. 2011, 73, 685–705. [CrossRef]

247. McHugh, D.; Gil, J. Senescence and aging: Causes, consequences, and therapeutic avenues. J. Cell Biol. 2018, 217, 65–77. [CrossRef]

248. Coppe, J.-P.; Desprez, P.-Y.; Krtolica, A.; Campisi, J. The senescence-associated secretory phenotype: The dark side of tumor suppression. Annu. Rev. Pathol. Mech. Dis. 2010, 5, 99–118. [CrossRef]

249. Freund, A.; Orjalo, A.V.; Desprez, P.-Y.; Campisi, J. Inflammatory networks during cellular senescence: Causes and consequences. Trends Mol. Med. 2010, 16, 238–246. [CrossRef]

250. Kim, Y.H.; Choi, Y.W.; Lee, J.; Soh, E.Y.; Kim, J.-H.; Park, T.J. Senescent tumor cells lead the collective invasion in thyroid cancer. Nat. Commun. 2017, 8, 1–14. [CrossRef]

251. Wangsa, D.; Quintanilla, I.; Torabi, K.; Vila-Casadesús, M.; Ercilla, A.; Klus, G.; Yuce, Z.; Galofré, C.; Cuatrecasas, M.; Lozano, J.J. Near-tetraploid cancer cells show chromosome instability triggered by replication stress and exhibit enhanced invasiveness. Faseb J. 2018, 32, 3502–3517. [CrossRef]

252. Mackenzie, K.J.; Carroll, P.; Martin, C.-A.; Murina, O.; Fluteau, A.; Simpson, D.J.; Olova, N.; Sutcliffe, H.; Rainger, J.K.; Leitch, A. cGAS surveillance of micronuclei links genome instability to innate immunity. Nature 2017, 548, 461–465. [CrossRef] [PubMed]

253. Ahn, J.; Xia, T.; Konno, H.; Konno, K.; Ruiz, P.; Barber, G.N. Inflammation-driven carcinogenesis is mediated through STING. Nat. Commun. 2014, 5, 5166. [CrossRef] [PubMed]

254. Rathje, L.-S.Z.; Nordgren, N.; Pettersson, T.; Rönndlund, D.; Widengren, J.; Aspenström, P.; Gad, A.K. Oncogenes induce a vimentin filament collapse mediated by HDAC6 that is linked to cell stiffness. Proc. Natl. Acad. Sci. USA 2014, 111, 1515–1520. [CrossRef] [PubMed]

255. Strouhalova, K.; Prechová, M.; Gandalovičová, A.; Brábek, J.; Gregor, M.; Rosel, D. Vimentin intermediate filaments as potential target for cancer treatment. Cancers 2020, 12, 184. [CrossRef]

256. Northey, J.J.; Przybyla, L.; Weaver, V.M. Tissue force programs cell fate and tumor aggression. Cancer Discov. 2017, 7, 1224–1237. [CrossRef]

257. Vasudevan, A.; Baruah, P.S.; Smith, J.C.; Wang, Z.; Sayles, N.M.; Andrews, P.; Kendall, J.; Leu, J.; Chunduri, N.K.; Levy, D. Single-chromosomal gains can function as metastasis suppressors and promoters in colon cancer. Dev. Cell 2020, 52, 413–428.e416. [CrossRef] [PubMed]

258. Flynn, P.J.; Koch, P.D.; Mitchison, T.J. Chromatin Bridges, not Micronuclei, Activate cGAS after Drug-induced Mitotic Errors in Human Cells. bioRxiv 2021. [CrossRef]

259. Ghadimi, B.M.; Sackett, D.L.; Difilippantonio, M.J.; Schrock, E.; Neumann, T.; Jauho, A.; Auer, G.; Ried, T. Centrosome amplification and instability occurs exclusively in aneuploidy, but not in diploid colorectal cancer cell lines, and correlates with numerical chromosomal aberrations. Genes Chromosomes Cancer 2000, 27, 183–190. [CrossRef]

260. Passerini, V.; Ozeri-Galai, E.; De Pagter, M.S.; Donnelly, N.; Schmalbrock, S.; Kloosterman, W.P.; Kerem, B.; Storchová, Z. The presence of extra chromosomes leads to genomic instability. Nat. Commun. 2016, 7, 10754. [CrossRef]

261. Duesberg, P. Are centrosomes or aneuploidy the key to cancer? Science 1999, 284, 2091–2092. [CrossRef] [PubMed]

262. Chan, J.Y. A clinical overview of centrosome amplification in human cancers. Int. J. Biol. Sci. 2011, 7, 1122–1144. [CrossRef] [PubMed]

263. Levine, M.S.; Bakker, B.; Boeckx, B.; Moyett, J.; Lu, J.; Vitre, B.; Spiersings, D.C.; Lansdorp, P.M.; Cleveland, D.W.; Lambrechts, D.; et al. Centrosome Amplification Is Sufficient to Promote Spontaneous Tumorigenesis in Mammals. Dev. Cell 2017, 40, 313–322.e315. [CrossRef]
264. Sercin, O.; Larsimont, J.C.; Karambelas, A.E.; Marthiens, V.; Marthiens, V.; Boeckx, B.; Le Mercier, M.; Lambrechts, D.; Basto, R.; Blanpain, C. Transient PLK4 overexpression accelerates tumorigenesis in p53-deficient epidermis. *Nat. Cell Biol.* 2016, 18, 100–110. [CrossRef] [PubMed]

265. Ganier, O.; Schnerr, D.; Oertle, P.; Lim, R.Y.; Plodinec, M.; Nigg, E.A. Structural centrosome aberrations promote non-cell-autonomous invasiveness. *EMBO J.* 2018, 37, e98576. [CrossRef]

266. Godinho, S.A.; Picone, R.; Burute, M.; Dagher, R.; Su, Y.; Leung, C.T.; Polyan, K.; Brugge, J.S.; Thery, M.; Pellman, D. Oncogene-like induction of cellular invasion from centrosome amplification. *Nature* 2014, 510, 167–171. [CrossRef]

267. Armandis, T.; Monteiro, P.; Adams, S.D.; Bridgeman, V.L.; Rajeeve, V.; Gadaleta, E.; Marzec, J.; Chelala, C.; Malanchi, I.; Cutilias, P.R. Oxidative stress in cells with extra centrosomes drives non-cell-autonomous invasion. *Dev. Cell* 2018, 47, 409–424.e409. [CrossRef]

268. Potapova, T.A.; Seidel, C.W.; Box, A.C.; Rancati, G.; Li, R. Transcriptome analysis of tetraploid cells identifies cyclin D2 as a facilitator of adaptation to genome doubling in the presence of p53. *Mol. Biol. Cell* 2016, 27, 3065–3084. [CrossRef]

269. Akino, T.; Hida, K.; Hida, Y.; Tsuchiya, K.; Freedman, D.; Muraki, C.; Ohga, N.; Matsuda, K.; Akiyama, K.; Harabayashi, T. Cytogenetic abnormalities of tumor-associated endothelial cells in human malignant tumors. *Am. J. Pathol.* 2009, 175, 2657–2667. [CrossRef]

270. Hida, K.; Hida, Y.; Amin, D.N.; Flint, A.F.; Panigrahy, D.; Morton, C.C.; Klagesbrun, M. Tumor-associated endothelial cells with cytogenetic abnormalities. *Cancer Res.* 2004, 64, 8249–8255. [CrossRef] [PubMed]

271. Kondoh, M.; Ohga, N.; Akiyama, K.; Hida, Y.; Maishi, N.; Towfik, A.M.; Inoue, N.; Shindoh, M.; Hida, K. Hypoxia-induced reactive oxygen species cause chromosomal abnormalities in endothelial cells in the tumor microenvironment. *PLoS ONE* 2013, 8, e80349. [CrossRef]

272. Jain, R.K. Molecular regulation of vessel maturation. *Nat. Med.* 2003, 9, 685–693. [CrossRef] [PubMed]

273. McDonald, D.M.; Baluk, P. Significance of blood vessel leakiness in cancer. *Cancer Res.* 2002, 62, 5381–5385. [PubMed]

274. Corver, W.E.; ter Haar, N.T.; Fleuren, G.J.; Oosting, J. Cervical carcinoma-associated fibroblasts are DNA diploid and do not show evidence for somatic genetic alterations. *Cell. Oncol.* 2011, 34, 553–563. [CrossRef] [PubMed]

275. Zheng, X.; Liu, Y.; Zhou, H.; Chen, Q.; Li, B. Analysis of chromosome karyotype of oral carcinoma-associated Fibroblasts. *West China J. Stomatol.* 2005, 23, 159–160. [CrossRef]

276. Dudley, A.C.; Shih, S.-C.; Cliffe, A.R.; Hida, K.; Klagsbrun, M. Attenuated p53 activation in tumour-associated stromal cells accompanies decreased sensitivity to etoposide and vincristine. *Br. J. Cancer* 2008, 99, 118–125. [CrossRef]

277. Pelham, R.J.; Rodgers, L.; Hall, I.; Lucito, R.; Nguyen, K.C.; Navin, N.; Hicks, J.; Mu, D.; Powers, S.; Wigler, M. Identification of alterations in DNA copy number in host stromal cells during tumor progression. *Proc. Natl. Acad. Sci. USA* 2006, 103, 19848–19853. [CrossRef]

278. Tuhanen, H.; Anttila, M.; Kosma, V.M.; Heinonen, S.; Juhola, M.; Helisma, S.; Kataja, V.; Mannermaa, A. Frequent gene dosage alterations in stromal cells of epithelial ovarian carcinomas. *Int. J. Cancer* 2006, 119, 1345–1353. [CrossRef]

279. Fukino, K.; Shen, L.; Matsumoto, S.; Morrison, C.D.; Mutter, G.L.; Eng, C. Combined total genome loss of heterozygosity scan of breast cancer stroma and epithelium reveals multiplicity of stromal targets. *Cancer Res.* 2004, 64, 7231–7236. [CrossRef]

280. Fukino, K.; Shen, L.; Patocs, A.; Mutter, G.L.; Eng, C. Genomic instability within tumor stroma and clinicopathological characteristics of sporadic primary invasive breast carcinoma. *JAMA* 2007, 297, 2103–2111. [CrossRef]

281. Groß, O.; Brummer, T.; Zeiser, R. Immune modulatory effects of oncogenic KRAS in cancer. *Nat. Commun.* 2020, 11, 5439. [CrossRef]

282. Thorsson, V.; Gibbs, D.L.; Brown, S.D.; Wolf, D.; Bortone, D.S.; Yang, T.-H.O.; Porta-Pardo, E.; Gao, G.F.; Plaisier, C.L.; Eddy, J.A. The immune landscape of cancer. *Immunity* 2018, 48, 812–830.e814. [CrossRef]

283. Ohashi, A.; Ohori, M.; Iwai, K.; Nakayama, Y.; Nambu, T.; Morishita, D.; Kawamoto, T.; Miyamoto, M.; Hirayama, T.; Okaniwa, M. Aneuploidy generates proteotoxic stress and DNA damage concurrently with p53-mediated post-mitotic apoptosis in SAC-impaired cells. *PLoS Genet.* 2012, 8, e1003232. [CrossRef] [PubMed]

284. Chang, S.-L.; Lai, H.-Y.; Tung, S.-Y.; Leu, J.-Y. Dynamic large-scale chromosomal rearrangements fuel rapid adaptation in yeast populations. *PLoS Genet.* 2013, 9, e1003232. [CrossRef] [PubMed]
292. Selmecki, A.; Forche, A.; Berman, J. Aneuploidy and isochromosome formation in drug-resistant Candida albicans. Science 2006, 313, 367–370. [CrossRef] [PubMed]

293. Yona, A.H.; Moran, Y.S.; Herbst, R.H.; Romano, G.H.; Mitchell, A.; Kupiec, M.; Pilpel, Y.; Dahan, O. Chromosomal duplication is a transient evolutionary solution to stress. Proc. Natl. Acad. Sci. USA 2012, 109, 21010–21015. [CrossRef]

294. Chen, G.; Bradford, W.D.; Seidel, C.W.; Li, R. Hsp90 stress potentiates rapid cellular adaptation through induction of aneuploidy. Nature 2012, 482, 246. [CrossRef] [PubMed]

295. Cai, Y.; Crowther, J.; Pastor, T.; Asbagh, L.A.; Baietti, M.F.; De Troyer, M.; Vazquez, I.; Talebi, A.; Renzi, F.; Dehairs, J. Loss of chromosome 8p governs tumor progression and drug response by altering lipid metabolism. Cancer Cell 2016, 29, 751–766. [CrossRef] [PubMed]

296. Xue, W.; Kitzing, T.; Roessler, S.; Zuber, J.; Krasnitz, A.; Schultz, N.; Revill, K.; Weissmueller, S.; Rappaport, A.R.; Simon, J. Chromosomal duplication is a transient evolutionary solution to stress. Proc. Natl. Acad. Sci. USA 2012, 109, 8212–8217. [CrossRef]

297. Dai, C.; Sun, F.; Zhu, C.; Hu, X. Tumor environmental factors glucose deprivation and lactic acidosis induce mitotic chromosomal instability—an implication in aneuploid human tumors. PLoS ONE 2013, 8, e63054. [CrossRef] [PubMed]

298. Ried, T.; Knutzen, R.; Steinbeck, R.; Blegen, H.; Schröck, E.; Heselmeyer, K.; du Manoir, S.; Auer, G. Comparative genomic hybridization reveals a specific pattern of chromosomal gains and losses during the genesis of colorectal tumors. Genes Chromosomes Cancer 1996, 15, 234–245. [CrossRef]

299. Weihua, Z.; Tsan, R.; Huang, W.-C.; Wu, Q.; Chiu, C.-H.; Fidler, I.J.; Hung, M.-C. Survival of cancer cells is maintained by EGFR number alterations dictate complex aneuploidy patterns. Genes Chromosomes Cancer 2016, 55, 1090–1101. [CrossRef] [PubMed]

300. Shukla, A.; Nguyen, T.H.; Moka, S.B.; Ellis, J.J.; Grady, J.P.; Oey, H.; Cristino, A.S.; Khanna, K.K.; Kroese, D.P.; Krause, L. Hsp90 stress potentiates rapid cellular adaptation through induction of aneuploidy. Nature 2016, 531, 492–497. [CrossRef] [PubMed]

301. Anatskaya, O.V.; Vinogradov, A.E. Somatic polyploidy promotes cell function under stress and energy depletion: Evidence from tissue-specific mammal transcriptome. Funct. Integr. Genom. 2010, 10, 433–446. [CrossRef] [PubMed]

302. Schoenfelder, K.P.; Fox, D.T. The expanding implications of polyploidy. J. Cell Biol. 2015, 209, 485–491. [CrossRef]

303. Galofré, C.; Gönül Geyik, Ö.; Asensio, E.; Wangsa, D.; Hirsch, D.; Parra, C.; Saez, J.; Mollà, M.; Yüce, Z.; Castells, A. Tetraploidy-associated genic heterogeneity confers chemo-radiotherapy resistance to colorectal cancer cells. Cancers 2020, 12, 1118. [CrossRef]

304. Schoenfelder, K.P.; Fox, D.T. The expanding implications of polyploidy. J. Cell Biol. 2015, 209, 485–491. [CrossRef]

305. Galofré, C.; Gönül Geyik, Ö.; Asensio, E.; Wangsa, D.; Hirsch, D.; Parra, C.; Saez, J.; Mollà, M.; Yüce, Z.; Castells, A. Tetraploidy-associated genic heterogeneity confers chemo-radiotherapy resistance to colorectal cancer cells. Cancers 2020, 12, 1118. [CrossRef]

306. Coward, J.; Harding, A. Size does matter: Why polyploid tumor cells are critical drug targets in the war on cancer. Front. Oncol. 2014, 4, 123. [CrossRef] [PubMed]

307. Ilidige, T.M.; Cragg, M.S.; Fringes, B.; Olive, P.; Erenpreisa, J.A. Polyploid giant cells provide a survival mechanism for p53 mutant cells after DNA damage. Cell Biol. Int. 2000, 24, 621–633. [CrossRef]

308. Donovan, P.; Cato, K.; Legaie, R.; Jayalath, R.; Olsson, G.; Hall, B.; Olson, S.; Bosor, S.; Reynolds, B.A.; Harding, A. Hyperdiploid tumors. Cell Biol. Int. 2014, 38, 116–128. [CrossRef]

309. Deleyrolle, L.P.; Harding, A.; Cato, K.; Siebzehnrubl, F.A.; Rahman, M.; Azari, H.; Olson, S.; Gabrielli, B.; Osborne, G.; Vescovi, A. Evidence for label-retaining tumour-initiating cells in human glioblastoma. Brain 2011, 134, 1331–1343. [CrossRef]

310. Illidge, T.M.; Cragg, M.S.; Fringes, B.; Olive, P.; Erenpreisa, J.A. Polyploid giant cells provide a survival mechanism for p53 mutant cells after DNA damage. Cell Biol. Int. 2000, 24, 621–633. [CrossRef]

311. Deleyrolle, L.P.; Harding, A.; Cato, K.; Siebzehnrubl, F.A.; Rahman, M.; Azari, H.; Olson, S.; Gabrielli, B.; Osborne, G.; Vescovi, A. Evidence for label-retaining tumour-initiating cells in human glioblastoma. Brain 2011, 134, 1331–1343. [CrossRef]

312. Schoenfelder, K.P.; Fox, D.T. The expanding implications of polyploidy. J. Cell Biol. 2015, 209, 485–491. [CrossRef] [PubMed]

313. Deleyrolle, L.P.; Harding, A.; Cato, K.; Siebzehnrubl, F.A.; Rahman, M.; Azari, H.; Olson, S.; Gabrielli, B.; Osborne, G.; Vescovi, A. Evidence for label-retaining tumour-initiating cells in human glioblastoma. Brain 2011, 134, 1331–1343. [CrossRef] [PubMed]
318. Zhang, Y.; Zhou, N.; Yu, X.; Zhang, X.; Li, S.; Lei, Z.; Hu, R.; Li, H.; Mao, Y.; Wang, X. Tumor macrophage: Macrophages transformed into tumor stem-like cells by virulent genetic material from tumor cells. *Onco Targets Ther.* 2017, 8, 8236. [CrossRef] [PubMed]

319. Clawson, G.A.; Matters, G.L.; Xin, P.; Imamura-Kawasawa, Y.; Du, Z.; Thiboutot, D.M.; Helm, K.E.; Neves, R.I.; Abraham, T. Macrophage-tumor cell fusions from peripheral blood of melanoma patients. *PLoS ONE* 2015, 10, e0134320. [CrossRef]

320. Bottoni, G.; Katarkar, A.; Tassone, B.; Ghosh, S.; Clocciachi, A.; Goruppi, S.; Bordignon, P.; Jafari, P.; Tordini, F.; Lunardi, T. CSL controls telomere maintenance and genome stability in human dermal fibroblasts. *Nat. Commun.* 2019, 10, 3884. [CrossRef] [PubMed]

321. Katarkar, A.; Bottoni, G.; Clocciachi, A.; Goruppi, S.; Bordignon, P.; Lazzaroni, F.; Gregnanin, I.; Ostano, P.; Neel, V.; Dotto, G.P. NOTCH1 gene amplification promotes expansion of Cancer Associated Fibroblast populations in human skin. *Nat. Commun.* 2020, 11, 5126. [CrossRef] [PubMed]

322. Santaguida, S.; Richardson, A.; Iyer, D.R.; M’saad, O.; Zasadil, L.; Knouse, K.A.; Wong, Y.I.; Rhind, N.; Desai, A.; Amon, A. Chromosome Mis-segregation Generates Cell-Cycle-Arrested Cells with Complex Karyotypes that Are Eliminated by the Immune System. *Dev. Cell* 2017, 41, 638–651.e5. [CrossRef] [PubMed]

323. Senovilla, L.; Vitale, I.; Martins, I.; Tailler, M.; Pailleret, C.; Michaud, M.; Galluzzi, L.; Adjemian, S.; Kepp, O.; Niso-Santano, M.; et al. An immunosurveillance mechanism controls cancer cell ploidy. *Science* 2012, 337, 1678–1684. [CrossRef]

324. Watson, E.V.; Elledge, S.J. Aneuploidy Police Detect Chromosomal Imbalance Triggering Immune Crackdown! *Trends Genet.* 2017, 33, 662–664. [CrossRef]

325. Davoli, T.; Uno, H.; Wooten, E.C.; Elledge, S.J. Tumor aneuploidy correlates with markers of immune evasion and with reduced response to immunotherapy. *Science* 2017, 355. [CrossRef]

326. Wang, R.W.; Viganò, S.; Ben-David, U.; Amon, A.; Santaguida, S. Aneuploid cells activate NF-κB to promote their immune clearance by NK cells. *bioRxiv* 2020. [CrossRef]

327. Granados, D.P.; Tanguay, P.L.; Hardy, M.P.; Caron, E.; de Verteuil, D.; Melloche, S.; Perreault, C. ER stress affects processing of MHC class I-associated peptides. *Bmc Immunol.* 2009, 10, 10. [CrossRef]

328. Zanetti, M.; Rodvold, J.J.; Mahadevan, N.R. The evolving paradigm of cell-nonautonomous UPR-based regulation of immunity by cancer cells. *Oncoogene* 2016, 35, 269–278. [CrossRef]

329. Tripathi, R.; Modur, V.; Senovilla, L.; Kroemer, G.; Komurov, K. Suppression of tumor antigen presentation during aneuploid tumor evolution contributes to immune evasion. *Oncoimmunology* 2019, 8, 1657374. [CrossRef]

330. McGranahan, N.; Rosenthal, R.; Heselmeyer-Haddad, K.; Patkar, S.; Hirsch, D.; Camps, J.; Brown, M.; Bronder, D.; Chen, W.-D.; Lokanga, R.; Gebhart, E.; Liehr, T. Patterns of genomic imbalances in human solid tumors. *System.* 2018, 29, 49–65. [CrossRef] [PubMed]

331. Rosenthal, R.; Cadieux, E.L.; Salgado, R.; Al Bakir, M.; Moore, D.A.; Hiley, C.T.; Lund, T.; Tanić, M.; Reading, J.L.; Joshi, K. Neoantigen-directed immune escape in lung cancer evolution. *Nature* 2019, 567, 479–485. [CrossRef] [PubMed]

332. Milo, I.; Bedora-Faure, M.; Garcia, Z.; Thibaut, R.; Périer, L.; Shakhar, G.; Deriano, L.; Bousso, P. The immune system profoundly restricts intratumor genetic heterogeneity. *Sci. Immunol.* 2018, 3, eaa4135. [CrossRef]

333. Hatzikiriou, H.; Basanta, D.; Simon, M.; Schaller, K.; Deutsch, A. ‘Go or grow’: The key to the emergence of invasion in tumour progression? *Math. Med. Biol. A J. Inst. Math. Biol.* 2012, 29, 49–65. [CrossRef] [PubMed]

334. Daoust, S.P.; Fahrig, L.; Martin, A.E.; Thomas, F. From forest and agro-ecosystems to the microecosystems of the human body: What can landscape ecology tell us about tumor growth, metastasis, and treatment options? *Ecol. Appl.* 2013, 6, 82–91. [CrossRef]

335. Kalluri, R.; Weinberg, R.A. The basics of epithelial-mesenchymal transition. *J. Clin. Investig.* 2009, 119, 1420–1428. [CrossRef] [PubMed]

336. Padilla-Nash, H.M.; McNeil, N.E.; Yi, M.; Nguyen, Q.T.; Hu, Y.; Wangsa, D.; Mack, D.L.; Hummon, A.B.; Case, C.; Cardin, E.; et al. Aneuploidy, oncogene amplification and epithelial to mesenchymal transition define spontaneous transformation of murine epithelial cells. *Carcinogenesis* 2013, 34, 1929–1939. [CrossRef]

337. Gao, C.; Su, Y.; Koeman, J.; Haak, E.; Dykema, K.; Essenberg, C.; Hudson, E.; Betillo, D.; Khoo, S.K.; Vande Woude, G.F. Chromosome instability drives phenotypic switching to metastasis. *Proc. Natl. Acad. Sci. USA* 2016, 113, 14793–14798. [CrossRef] [PubMed]

338. Bakhous, S.F.; Cantley, L.C. The multifaceted role of chromosomal instability in cancer and its microenvironment. *Cell* 2018, 174, 1347–1360. [CrossRef]

339. Gebhart, E.; Liehr, T. Patterns of genomic imbalances in human solid tumors. *Int. J. Oncol.* 2000, 16, 383–428. [CrossRef] [PubMed]

340. Auslander, N.; Heselmeyer-Haddad, K.; Patkar, S.; Hirsch, D.; Camps, J.; Brown, M.; Bronder, D.; Chen, W.-D.; Lokanga, R.; Wangsa, D. Cancer-type specific aneuploidies hardwire chromosome-wide gene expression patterns of their tissue of origin. *BioRxiv* 2019, 563858. [CrossRef]

341. Foley, J.W.; Zhu, C.; Jolivet, P.; Zhu, S.X.; Lu, P.; Meaney, M.J.; West, R.B. Gene expression profiling of single cells from archival tissue with laser-capture microdissection and Smart-SEQ. *Genome Res.* 2019, 29, 1816–1825. [CrossRef] [PubMed]

342. Rozenblatt-Rosen, O.; Regev, A.; Oberdoerffer, P.; Nawy, T.; Hupalowska, A.; Rood, J.E.; Ashenberg, O.; Cerami, E.; Coffey, R.J.; Demir, E. The Human Tumor Atlas Network: Charting Tumor Transitions across Space and Time at Single-Cell Resolution. *Cell 2020*, 181, 236–249. [CrossRef]

343. Natraj, R.; Saiml, H.; Mardakheh, F.K.; Garcia, M.A.; Tape, C.J.; Dowsett, M.; Bakal, C.; Yuan, Y. Microenvironmental heterogeneity parallels breast cancer progression: A histology—genomic integration analysis. *PLoS Med.* 2016, 13, e1001961. [CrossRef] [PubMed]

344. Meadows, D.H. *Leverage Points: Places to Intervene in a System*; Sustainability Institute: Hartland, VT, USA, 1999.