MINI REVIEW

Therapeutic targeting of cellular stress responses in cancer
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Abstract
Similar to bacteria, yeast, and other organisms that have evolved pathways to respond to environmental stresses, cancer cells develop mechanisms that increase genetic diversity to facilitate adaptation to a variety of stressful conditions, including hypoxia, nutrient deprivation, exposure to DNA-damaging agents, and immune responses. To survive, cancer cells trigger mechanisms that drive genomic instability and mutation, alter gene expression programs, and reprogram the metabolic pathways to evade growth inhibition signaling and immune surveillance. A deeper understanding of the molecular mechanisms that underlie the pathways used by cancer cells to overcome stresses will allow us to develop more efficacious strategies for cancer therapy. Herein, we overview several key stresses imposed on cancer cells, including oxidative, metabolic, mechanical, and genotoxic, and discuss the mechanisms that drive cancer cell responses. The therapeutic implications of these responses are also considered, as these factors pave the way for the targeting of stress adaptation pathways in order to slow cancer progression and block resistance to therapy.

Introduction
All living things experience adverse conditions at some point during their lifespan.1–5 Plants and animals are subjected to abiotic and biotic stresses that include salt,6–11 drought,12–15 and pathogens.16–20 Environmental stresses also affect organisms at the cellular level. For example, cancer cells must adapt to both intracellular and extracellular stress, such as hypoxia, starvation, exposure to anticancer drugs, and immune responses.21–23 Single-celled organisms, including bacteria and yeast, have developed mechanisms to survive in the face of environmental stresses by promoting mutagenesis, thereby increasing genetic diversity.24–29 These adaptations involve increased genomic instability and mutation, coupled with changes to signaling pathways and gene expression programs, creating an intricate network that researchers have been trying to unravel in recent years.30–35 Uncovering the molecular mechanisms by which plants and microorganisms respond to stresses will help us to better understand biological evolution.36–41 Insights from these studies could impact a wide variety of fields, ranging from the identification of phenotypic traits to improve crop tolerance to extreme conditions, to the design of more effective therapeutic strategies for cancer.42

The location and type of malignancy greatly affect the duration and type of stress experienced by cancer cells.43–46 For example, solid tumors residing in a confined space are more likely to experience insufficient oxygen and nutrient supply, in addition to physical compression.47–50 In this review, we focused on responses to oxidative, metabolic, mechanical, and genotoxic stresses in solid cancers, as well as the therapeutic implications of these responses. Recent advances in cancer cell stress responses have the potential to lead to new advances in cancer therapy.

Oxidative stress
Reactive oxygen species (ROS), such as superoxide anion radicals, hydroxyl radicals, and hydrogen peroxide, are natural by-products of aerobic metabolism.51–57 In cells, mitochondria are the primary source of endogenous intracellular reactive species. These metabolic intermediates play important roles in physiological functions and signaling pathways, both as effectors and as signaling molecules.58–62 However, because of the potential toxic impact on key cellular...
components (e.g. DNA, lipids, and proteins) and even the induction of apoptosis, redox homeostasis must be tightly controlled. ROS production must be balanced with ROS removal by scavengers (e.g. glutathione peroxidase, thioredoxins, superoxide dismutases).\textsuperscript{53–66} However, cancer cells are often present in a hypoxic microenvironment that promotes increased metabolic activity and oncogene stimulation. As a result, these cells are characterized by higher levels of ROS and are more prone to oxidative stress.\textsuperscript{60,68} To survive, cancer cells mobilize a number of adaptive mechanisms, such as activation of ROS-scavenging systems and the suppression of cell death factors.

Although a large body of research has shown that oxidative stress can promote cancer initiation, progression, metastasis, and resistance to anticancer agents, recent studies have shed new light on the negative effects of excessive ROS levels on cancer cell survival. Results from these studies suggest that upregulated production of ROS in cancer cells could be harnessed to induce apoptosis or necrosis for therapeutic purposes.\textsuperscript{69,70} A number of drugs are reported to enhance cellular oxidative stress, either by directly increasing intracellular ROS levels or through inhibition of the antioxidant enzyme system. For example, the anticancer drug arsenic trioxide has been shown to induce programmed cell death via multiple effects on tumor cells, including the upregulation of ROS levels and Bax expression and the downregulation of nuclear factor kappa B activity and microtubule polymerization.\textsuperscript{71,72} As the potential for harnessing ROS for the treatment of cancer is increasingly being recognized, drugs that act to induce oxidative stress are under active investigation in preclinical studies and clinical practice. However, our understanding of the role of oxidative stress in cancer treatment is far from sufficient, especially with respect to the anticancer effects of different levels of ROS in the body.\textsuperscript{73} Quantitative studies are urgently needed to elucidate the details of the “yin and yang” of ROS and to understand the transition between their cancer-promoting and anticancer effects. As a result, we are still a long way from the widespread clinical application of ROS boosters in cancer therapy.

**Metabolic stress**

Metabolism reprogramming is an emerging hallmark of cancer. Most cancers are characterized by aerobic glycolysis (termed the Warburg effect). In addition, glutamine addiction has been recognized in some cancer cells, and mitochondrial dysfunction has been observed in cancer cells harboring a metastatic phenotype.\textsuperscript{74,75} Metabolism reprogramming is a cellular adaptation to metabolic stress induced by oncogene expression (e.g. MYC) and stimuli from the tumor microenvironment.\textsuperscript{76} Reprogramming occurs when the metabolic network cannot meet the energetic and material demands required for the large number of physiological activities conducted simultaneously in cancer cells.\textsuperscript{77–79} Conflicts arise when the metabolic network attempts to coordinate the priorities of all “apparently essential” metabolic pathways, giving rise to metabolic stress. To deal with these stresses, cancer cells hijack the mechanisms used by normal cells to sense nutrient/energy status and make adaptations.\textsuperscript{80} The process typically involves changes in nutrient-sensing pathways that are regulated by AMP-activated protein kinase (AMPK) and mammalian target of rapamycin (mTOR), as well as stress response pathways, such as the endoplasmic reticulum (ER) stress response and autophagy.\textsuperscript{80}

The metabolic stress response network includes a number of regulatory enzymes and transcription factors (e.g. AMPK, HIF\textsubscript{a}, PGC1\textalpha), providing a wide variety of options for pharmaceutical targeting.\textsuperscript{81} For example, in the case of MYC-induced metabolic stress, inhibitors of glutaminase and lactate dehydrogenase have been shown to suppress tumor growth by blocking the flux of the nutrients required for cancer cell proliferation in response to upregulated MYC activity.\textsuperscript{81,82} Similarly, manipulating the response pathways involved in adaptation to MYC-induced metabolic stress has been also considered as a therapeutic option. Targeting the ARK5/AMPK axis was shown to be effective in a hepatocellular carcinoma model, and inhibition of IRE1/XBP1 was promising in triple-negative breast cancer.\textsuperscript{83} Although a number of experimental studies have suggested the potential of various metabolic pathway inhibitors, these drugs have shown limited efficacy in the single agent setting.\textsuperscript{84} To improve efficacy, combination therapies using multiple metabolic inhibitors in an optimized formulation or metabolic therapy coupled with standard therapy likely represent better options.

**Mechanical stress**

With the increasing availability of innovative tools capable of measuring, visualizing, and mimicking the mechanical forces exerted on cancer cells, the emerging field of cellular biomechanics has enhanced our understanding of cancer biology.\textsuperscript{85–89} There are three major types of mechanical stresses experienced by cancer cells: tensile, compressive, and shear. Tensile stress arises from cellular actomyosin contraction in response to extracellular matrix (ECM) stiffness.\textsuperscript{90–94} Compressive stress takes place as the tumor grows within a confined space. Shear stress is elicited by the flow of blood and interstitial fluid around cancer cells. To produce transient cellular responses, mechanical stresses are sensed and transduced to generate biochemical signals via a process called mechanotransduction.\textsuperscript{95} This process involves mechanosensors (e.g. integrin receptors, mechanically activated ion channels, catenins), their
immediate downstream signaling molecules (e.g. focal adhesion kinase [FAK], SRC, phosphoinositide 3-kinase, Rho/Rho kinase, growth factor receptors, G protein-coupled receptors), and adapter/linker proteins that relay signals to the actin and microtubule cytoskeleton networks.\textsuperscript{96} By virtue of reorganization of the cytoskeleton, cancer cells can change their contractility and intracellular tension to adapt to mechanical stresses.\textsuperscript{97} In addition to activation of these signaling pathways, changes in gene expression (e.g. ECM proteins, cytoskeletal proteins) can lead to sustained cellular responses through modification of the tumor microenvironment and changes in the mechanical properties of cancer cells. Within the tumor microenvironment, cancer cells are constantly exposed to different mechanical stresses, which are now being recognized as contributors to tumor growth and metastasis.\textsuperscript{98–100}

Therefore, the associated signaling and gene expression pathways, particularly those molecular hubs that integrate multiple pathways, represent potential therapeutic targets.

Examination of completed/ongoing pre-clinical studies and clinical trials reveals that targeting of cell contractility, solid stress, and ECM stiffness are currently the three primary therapeutic strategies under evaluation.\textsuperscript{101,102} Drugs used to modulate cell contractility include (but are not limited to) ruxolitinib (a janus kinase inhibitor), fasudil (an Rho-associated kinase inhibitor), and a number of FAK inhibitors.\textsuperscript{103} Of note, FAK inhibition has been extensively tested as a therapeutic strategy to inhibit cell contractility in a variety of solid tumors; 10 clinical trials have been completed, and results are pending. To target solid stress, hyaluronidases and angiotensin inhibitors have been investigated. Mechanistically, hyaluronidases (e.g. pegvorhyaluronidase alfa) have been shown to improve tissue compliance by degrading the ECM protein hyaluronan to release immobilized fluid.\textsuperscript{99} By causing dilation of the vasculature and reduction in blood pressure, angiotensin inhibitors (e.g. losartan) can effectively decrease interstitial fluid pressure, enabling improved perfusion and therapeutic efficacy.\textsuperscript{104} The strategy of modulating ECM stiffness to treat cancer is more suitable for solid tumors, like breast cancer, and has been tested with celecoxib (a cyclooxygenase-2 inhibitor), \(\beta\)-aminopropionitrile (a lipoxigenase inhibitor), and the combination of transforming growth factor-\(\beta\) and hedgehog signaling inhibitors.\textsuperscript{105,106} Although targeting the mechanical drivers of tumor progression is a promising therapeutic approach, the observed limitations, including low efficacy, still need to be addressed based on our accumulating knowledge of the mechanical stress response in cancer cells.

**Genotoxic stress**

Cancer cells can undergo genotoxic stress as a result of threats to DNA structure and genome instability.\textsuperscript{107–111} The threats can arise from a broad range of events and agents, including unresolved replication fork stalling during normal DNA replication, accumulation of metabolic intermediates (e.g. ROS) that are highly reactive to DNA, and exposure to chemotherapy or radiation therapy.\textsuperscript{112–118} Replication stress can occur even under normal physiological conditions in cancer cells because of a shortage of building blocks (histones, deoxyribonucleotide triphosphates), conflicts between concurrent activation of the massive replication and transcription machineries, as well as unusual DNA structures and topologies.\textsuperscript{119,120} As a result of replication fork stalling, levels of exposed single-stranded DNA increase, thereby recruiting RPA (a single-stranded DNA-binding protein) to the lesion. Binding of RPA is followed by the recruitment of the protein kinase ATR to activate the ATR-CHK1 axis. Although this process is usually referred to as the replication stress response (RSR), the ATR-CHK1 axis is also integrated into a more complex signal transduction pathway termed the DNA damage response (DDR), which includes multiple cell cycle checkpoints that dictate the fate of cancer cells depending on whether the damage can be repaired.\textsuperscript{121–123}

A number of chemotherapeutic drugs exert stress on the cancer genome, most of which act as genotoxins that damage the DNA and induce the DDR; these include DNA cross-linkers, topoisomerase poisons, and alkylating agents.\textsuperscript{124–126} Although conventional anticancer agents were developed to selectively target highly proliferative cancer cells over normal cells, highly proliferative normal tissues (e.g. bone marrow, gut epithelium) are also targeted, and the side effects can sometimes be life-threatening. Fortunately, the emergence of targeted drugs with improved specificity and fewer side effects have provided another option for patients and clinicians. For example, olaparib is an inhibitor of poly(ADP-ribose) polymerases that was first approved for the treatment of advanced ovarian cancers harboring BRCA1/2 mutations. In addition to targeting DDR, manipulating the RSR has also been considered for application in cancer therapy.\textsuperscript{127–129} Currently, three classes of inhibitors that aim to enhance replication stress in cancer therapy are under consideration: ATR, CHK1, and Wee1 inhibitors. Importantly, preclinical studies have shown that many of these RSR inhibitors exhibit synergistic effects with conventional chemotherapies and are thus under evaluation in series of clinical trials.\textsuperscript{130–133}

**Future perspectives**

Cancer cells reside in a dynamic microenvironment where they are under the influence of diverse stresses that shape tumor behavior. As a result, simplified models linking individual cellular stresses to cancer progression should be viewed with caution. Another layer of complexity arises...
from the crosstalk between different cellular responses. For example, excessive ROS levels play a role in oxidative and metabolic stress, as well as in genotoxic stress. In the future, it will be interesting to define the precise levels of ROS required to trigger a specific stress response or responses. Moreover, if we consider drug resistance of cancer cells as a type of cellular adaptation to harsh conditions, we may be able to apply our understanding of stress responses to develop improved strategies to target drug-resistant cancer cells. In recent years, the application of cancer immunotherapies has tremendously increased, and the cellular responses to immune inhibitors/activators and antibody-based drugs are in urgent need of characterization.

In the future, more efficacious therapeutic strategies may be designed based on the targeting of cellular stress responses or by combining stress-targeted therapies with standard/conventional therapy. The effectiveness of such agents depend on an improved understanding of stress responses in cancer cells.

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Disclosure

No authors report any conflict of interest.

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