10. Hypotheses of Carcinogenesis—The Atavistic Theory

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Abstract A deep comprehension of what cancer is as a biological phenomenon is lacking. Several theories have been proposed and many of them do not necessarily contradict each other. One of the theories is the intriguing hypothesis that a cancer cell may be triggered by mutations, but is basically a self-activated throwback to an ancestral cell phenotype running its ancient core functionality by preserving its vital functions, such as survival and uncontrolled proliferation.

Keywords ancestral cell phenotype | core functionality | atavism

After decades of extensive research, our knowledge of the carcinogenic process has grown. Cancer is currently widely regarded as random oncogenic mutations accumulating in cells, leading to an evolutionary process of emerging hallmarks (Hanahan and Weinberg 2011) that are reminiscent of unicellular organisms. However, a deeper comprehension of what cancer is as a biological phenomenon is still lacking. Several theories have been proposed and many of them do not necessarily contradict each other.

One of the theories is the intriguing hypothesis that a cancer cell is a throwback to an ancestral cell phenotype. That essential idea was proposed in 1914 by Theodor Boveri, who characterized the malignant tumor cell as a previously normal and “altruistic” tissue cell changed into an “egoistical” mode with loss of functions. The latter cell had lost normal reactivity to the rest of the body by releasing its multiplication from restraint and tending toward primitive, unicellular properties (Boveri 2008). In recent decades, essential elements of Boveri’s idea have been resurrected in an atavistic hypothesis of cancer which regard cancer as an ancient and systematic program of emergency survival procedures that preserves the two most vital core functions—survival and proliferation—in response to a damaging environment. Since cell survival and proliferation is deeply integrated in normal cell
physiology, upregulated genes coding for these normal traits are more likely to escape rather than alarm the immune system’s surveillance, which is one of the hallmarks of carcinogenesis. The hypothesis further suggests that carcinogenesis may be triggered by mutations, but its basic cause is a self-activation of a very old, programmed and deeply embedded toolkit of emergency survival programs (Davies and Lineweaver 2011). Evidence supporting this hypothesis has long remained non-observational, until recently.

More than one hundred years ago, William Coley noticed that some cancer patients showed spontaneous remission following severe infection (Hoption Cann et al. 2003). The traditional explanation was that infection boosted the reactions of the immune system, which then destroyed the cancer by chance. The atavistic hypothesis, on the other hand, proposes that at least part of the reason for Coley’s results is that cancer tumors are more vulnerable to infection than the rest of the body because, via their throwback to the ancestral phenotype, they have decoupled from the adaptive immune system. In other words, the tumor has regressed to an immunocompromised state and is thereby left unprotected against infection.

The role of immune system cells in carcinogenesis has been studied for decades, and the particular importance of the adaptive immune system has been unraveled. The basic idea behind immunotherapy, which has received increasing attention as a new way to combat cancer, is to boost the body’s immune system—both the innate and the adaptive—through a diversity of sophisticated strategies in order to improve the immune response against cancer (Dempke et al. 2017). The early results are encouraging; combinations of immunotherapy, novel targeted therapies, and conventional chemotherapy might be especially promising. Nevertheless, additional basic, translational and clinical studies with long follow-up time are crucial to unraveling immunotherapy as a breakthrough in cancer treatment.

Another discovery made by Otto Warburg a century ago showed that cancer cells often switch to fermentation, especially when the oxygen tension is low and the glucose concentration is high (Otto 2016). Fermentation processes create less energy but more biomass compared to normal human cells, which use oxygen to generate energy. The atavistic hypothesis seems to suggest that the ancestral cancer cells have proliferative advantages in low oxygen surroundings, since they are reversed to the evolutionary time more than one billion years ago when the first multicellular organisms evolved in a far less oxygen-rich atmosphere. Based on the Warburg effect, hyperbaric oxygen combined with a low-glucose have been studied in vitro and in patient trials. The mechanisms are complex and combinations of graded oxygen-glucose concentrations with novel therapeutics need to be studied in further detail.
The majority of cancers follow a predictable pattern of clinical development: a tumor grows in an organ, and if it is not cured, some of the cancer cells leave the primary tumor, spread via lymph or blood and invade remote organs, where they create metastases. Metastatic cancers are often beyond being cured and the vast majority of patients who die from cancer die from their metastases, not from their primary tumors. Cancer development goes through several distinctive functional hallmarks, including survival of the neoplastic cells, uncontrolled proliferation, increased motility, evasion of the immune system, and establishment of its own blood supply (Hanahan and Weinberg 2011). All these traits improve the survival and sustainability of the cancer cells over a relatively short period of time. The somatic mutation theory has challenges in explaining how random mutations accumulating in cells over time can confer so many improved functions in a single tumor. It also seems paradoxical that increasingly damaged genomes are able to code for proteins, resulting in gained functions in such a systematic and predictable behavior, acquiring the various hallmarks. Further, the non-neoplastic cells in a tumor—i.e. the non-mutated cells of the microenvironment—have shown tremendous impact on the overall survival of cancer patients. The predictable way that cancer progresses through its various stages of malignancy, both clinical and pathophysiological, indicates that cancer is not a case of randomly, damaged cells but a primitive cellular defense mechanism consisting of a systematic, programmed strategy as a response to environmental challenges.

Paul Davies, director of the Beyond Center for Fundamental Concepts in Science at Arizona State University, USA, describes the atavistic theory of cancer as a default state in which a cell under threat runs on its ancient core functionality, thereby preserving its vital functions, of which survival and uncontrolled proliferation is the most ancient, most vital and best preserved (Davies and Line-weaver 2011).

They have brought novelty to the atavistic theory through phylostratigraphic studies of the ages of genes by comparing how gene sequences diverge across many species, thereby enabling them to trace the evolutionary origin of genes involved in carcinogenesis (Bussey et al. 2017). In the general phylogenetic tree, the most widespread properties of the different organisms are usually the oldest, and can often be traced back to a common ancestor in the distant past. The atavistic theory hypothesizes that the oncogenes are clustered around the age of onset of multicellular organisms. The earliest traces of unicellular life can be dated back about 3.5 billion years and the onset of multicellularity first emerged about 1.5 billion years
ago. Through using gene databases, they found that evolutionary roots of cancer can be traced back to the early transitional phase from unicellularity to multicellularity, about 600 million years ago, before complex metazoans emerged. An estimation of the evolutionary ages of the genes in the human genome showed that genes younger than about 500 million years were more likely to be mutated in cancer, while genes older than a billion years tended to have fewer mutations than average. This is in accordance with the atavistic theory’s prediction that older genes are likely to be less mutated than younger genes in cancer, since the oldest genes are expected to be responsible for the ancient core functions of the aggressive cancer cell. A comprehensive study has recently characterized cancer driver genes and mutations from several thousand tumor exomes (Bailey et al. 2018); another study shows that older genes are expressed at higher levels when cancer progresses to a more aggressive and advanced stage (Trigos 2019).

By investigating the functionality of the oncogenes, they have shown that genes older than 950 million years are strongly enriched for two core functions: control of the cell cycle, and repair of DNA double-strand breaks (Cisneros et al. 2017). The evolutionary history of these genes revealed that cancer genes implicated in DNA repair match up with mutated genes in stressed bacteria employed for a critical survival function. These ancient and essentially identical genes, discovered in the DNA of bacteria and cancer, are known to be associated with poor patient prognosis. Elevated mutation rates in neoplastic cells are among the main reasons why chemotherapy falters when neoplasms evolve drug-resistant variants.

Other phylostratigraphic studies suggests a link between cancer genes and the emergence of multicellular life. By analyzing the expression profile of xenograft tumors at different stages and various tumor samples, Chen et al. demonstrated an evolving convergence from multicellular state towards unicellular state in cancer expression profile and functional status (Chen et al. 2018) Although together these evidences demonstrated a general trend toward atavism in carcinogenesis, there are still large elements of the atavistic hypothesis that remain unanswered. In particular, the answer as to whether cellular atavism from multicellularity to unicellularity is the cause or the result of carcinogenesis remains elusive.

**GENE EXPRESSION INFORMATION FROM THE NOWAC STUDY**

Mutations induce disturbed gene regulatory networks at a very early stage in the carcinogenic process, leading to changes in the flow of signals between genes and between cells. The Norwegian Women and Cancer Study, NOWAC (Lund et al.
2008) is trying to identify early carcinogenic signatures of these gene network changes in blood. We aim to identify distinct gene signature hallmarks of cancer in white blood cells that may precede the clinically noticeable changes in tumor cells and tissues, thus providing an early warning of upcoming cancer.

In Chapter 8 we identified a gene profile in white blood cells in those women who died from their cancer within a few years. Some of these signals are upregulated, pre-vertebrate genes maintaining core functions such as survival, maintenance of cytoskeleton, proliferation, cilia orientation, nuclear membrane proteins, DNA damage repair, and oxygen utilization (Table 9.1). The intriguing finding—that the signals from the white blood cells disappeared after a short time—might be a result of decoupling and thereby a default surveillance of the aggressive, ancestral phenotype of the cancer cells by the phylogenetically more novel adaptive immune system. At the time of diagnosis, another study showed no strong correlation between genes expressed in cancer tissue compared to white blood cells, except for some highly immunogenic breast cancer subgroups (Dumeaux et al. 2017).

These findings are essentially in accordance with the atavistic hypothesis showing that white blood cells’ responses to cells under threat run their core functionalities, preserving its most vital functions. These data are exclusively from GeneCards®. They should be further analyzed in comprehensive, inventory databases and applied by gene classification tools organizing genes around their function.

| Gene       | Function                                                                                           |
|------------|---------------------------------------------------------------------------------------------------|
| Significant upregulated genes | Mainly basic cell functions like cytoskeleton, cilia orientation, DNA damage, oxygen utilization |
| CCM2       | Cerebral Cavernous Malformations 2 is required for normal cytoskeletal structure, cell-cell interactions, and lumen formation in endothelial cells. |
| C14orf45   | May act by mediating a maturation step that stabilizes and aligns cilia orientation.               |
| ARL4A      | ADP Ribosylation Factor Like GTPase 4A is related to Mesodermal Commitment Pathway. Gene Ontology annotations related to this gene include GTP binding and GTPase activity. An important paralog of this gene is ARL4C. |
| LOC650898  | Involved in inducing the expression of cellular antiviral genes, including the interferon-β gene, in response to Pattern Recognition Receptors which modulate the strength and duration of the innate immune responses. |
**CBX3** This protein is recruited to sites of DNA damage and double-strand breaks. This protein can bind lamin B receptor, an integral membrane protein found in the inner nuclear membrane.

**C5orf30** May play a role in cilia membrane localization via its interaction with UNC119B and protein transport into photoreceptor cells.

**FSTL4** follistatin Like 4 shows Gene Ontology annotations related to calcium ion binding. Prognostic marker in pancreatic cancer. An important paralog of this gene is FSTL5.

**BPGM** The protein 2,3-diphosphoglycerate (2,3-DPG) is a small molecule found at high concentrations in red blood cells, where it binds to and decreases the oxygen affinity of hemoglobin. Deficiency of this enzyme increases the affinity of cells for oxygen.

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