Cell Cycle 14:16, 2547–2548; August 15, 2015; © 2015 Taylor & Francis Group, LLC

Stem cell division theory of cancer

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Understanding where and how cancer develops is important to reduce cancer incidence and mortality. According to the prevailing model of carcinogenesis, often called the somatic mutation theory, cancer is primarily caused by the accumulation of genetic mutations. Although many cancer-related genes have been discovered and their mutations precisely defined, this model can no longer interpret the genomic complexity the disease.[1] The cells in which these mutations occur also remain elusive. In addition, the somatic mutation theory cannot accommodate experimental and observational studies linking non-genotoxic factors to cancer.[2] Alternative and complementary theories of carcinogenesis are growing, such as the tissue organization field theory (summarized as "development gone awry") and the cancer stem cell model.[2-4] The cancer stem cell model proposes that cancer stem cells (CSCs) play a crucial role in tumor growth, metastasis and resistance to treatment; however, it remains uncertain the origin of these cells, or whether the model applies to few or many cancers.[3,4]

A research perspective recently published in *Oncoscience* provides an analysis that may help explain important aspects of the disease, such as the cellular origin of cancer, the striking variations in cancer incidence with age, or the existence of metastatic cancers in the absence of primary tumors.[5] Here I extend such an analysis and discuss a model of carcinogenesis that integrates some features from the existing models and may provide a better framework for understanding the disease.

The stem cell division theory proposes that (1) cancer arises from normal stem cells; (2) the main determinant for cancer development is the acquisition of damage in stem cells during their division; (3) the accumulation of enough damage in stem cells results in the generation of CSCs, which are responsible for tumor formation; (4) metastasis occurs when stem cells (deregulated, premalignant or cancerous) or their malignant progeny leave their natural tissue (not necessarily a primary tumor) and form tumors in other locations.[5]

Aging is responsible for most human cancers. For example, lung cancer is the most common cancer in the world and, according to SEER Cancer Statistics Review 1975–2012, the probability of being diagnosed with lung cancer is 0.01% (1 in 10000) in people under 30 y old and 6.20% (1 in 16) in people over 60 y old. This huge increase in cancer incidence in aged people indicates that the majority of human cancers develop because our cells accumulate damage as we age. DNA is the only cellular component able to accumulate damage during our whole life, and stem cells are the only cells that transmit our DNA from the zygote to the cells we have at the time of death. The rest of the cells (i.e., progenitor cells and terminally differentiated cells) cannot keep our DNA from the beginning of life until a possible cancer is formed. They receive our DNA from stem cells at different stages of life, but this DNA is lost when they are replaced by new cells. This strongly suggests that most human cancers arise from stem cells.[5]

According to this theory, cell division is crucial not only for tumor growth but also for the malignant transformation of normal stem cells; this is important to understand and prevent the disease. Cell division is a complex biological process in which many things can go wrong. Dividing cells are exposed, for example, to unavoidable mistakes made by DNA polymerases during DNA replication, or to stochastic failures in the distribution of cellular components between the daughter cells. In addition, dividing cells are particularly sensitive to the genotoxic and non-genotoxic damage induced by endogenous and exogenous carcinogens. It is well known that some tissues give rise to cancers millions of times more often than other tissues, and recent evidence suggests that the risk of developing cancer in a tissue can be explained by the number of normal stem cell divisions taking place in that tissue.[6] This finding not only supports the idea of cancer arising from stem cells, but also that stem cell division is the main determinant for cancer development.[5]

Understanding carcinogenesis requires the consideration of additional aspects. The fact that DNA is the only cellular component able to accumulate damage during our whole life does not mean that cancer is only caused by the accumulation of genetic mutations. It is important to recognize that cells can accumulate other types of carcinogenic DNA alterations, including mutations in non-coding DNA sequences, epigenetic changes, and chromosome alterations. It is also essential to realize that non-genotoxic cellular damages may cause DNA alterations. Damages in any cellular component involved in the elimination or detoxification of genotoxic agents, or in the repair of the DNA damage induced by these agents, may cause permanent DNA alterations. For example, any damage that reduces the functionality of ABC transporters may cause DNA alterations by reducing the capacity of these transmembrane

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Submitted: 05/27/2015; Revised: 05/28/2015; Accepted: 06/11/2015
http://dx.doi.org/10.1080/15384101.2015.1062330
Comment on: Lopez-Lazaro M. The migration ability of stem cells can explain the existence of cancer of unknown primary site. Rethinking metastasis. Oncoscience 2015, 2(5):467-75; PMID:26097879.

proteins to pump genotoxic agents out of the cells. Agents that do not cause direct cellular damage may also induce DNA alterations by activating cell division; cell division is associated with stochastic mistakes (e.g., DNA replication mistakes) that may originate heritable DNA alterations. It should also be noted that stem cells are established in niches, which protect the stem cells and regulate their biological properties, including their division rates and migration ability. Any factor (e.g., mechanical, physical, chemical or neural) disrupting the complex interactions between stem cells and their niches may alter their biological behavior and may facilitate cancer development.[7] This may explain why a variety of these factors can induce cancer or modify the risk of developing the disease.[2] For example, tissue injury is known to activate stem cell division for repair, and experimental and observational studies link tissue injury to cancer.[5]

This theory implies that cancer prevention can be achieved by avoiding factors that either induce damage to stem cells or increase their division rates. Cancer prevention can also be accomplished by stopping or delaying the process by which normal stem cells become CSCs, e.g., *via* chemoprevention. Curative cancer therapy requires the elimination of CSCs.[5]

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