

A New Hallmark of Cancer: Stemness

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Abstract.

Background. The term ‘cancer’ often describes malignant tumors. The issue of cancerous stem cells is not a novelty but has existed for centuries. Different civilizations have handled the stem cell subject depending on the knowledge at hand. A hallmark is a distinguishing factor that separates cancers from other conditions. Hence, there have been arguments about the exclusion or inclusion criteria for the six original hallmarks. This review will introduce stemness as a new hallmark for cancer and argue why it should get included. Thus, future studies will focus on how the tumor microenvironment can get used to fight cancer.

Methodology. A methodology of literature search using "stemness" as the keyword gets used in the review to avoid biasedness.

Results. Stem cells can undergo physiological changes to form malignant cells. Cancer cells are in a variety of cells in the body. The microenvironment of the tumor cells promotes their progression by nourishing them.

Conclusions. The results imply that stemness is the behavior of stem cells to self-renew and differentiate to form cells in all organisms. Stem cells are present in all types of hematological and solid cancers. It means that a problem in the self-renewal or differentiation process can lead to the formation of tumors or tumorigenic.

Introduction

It is essential to note that cancer existed long before its discovery. Ancient scholars proposed that the disease had no cure, but their knowledge of stem cells was limited. The invention of the microscope in the 19th century enabled efficient tissue screening. Thus, scientists formulated that hallmarks are principles that attempt to explain the complicated nature of the neoplastic disease. Stemness is the hallmark, which provides a cellular framework where genetically and phenotypically healthy cells change and become malignant. The Six hallmarks are: maintaining proliferative signaling, evading growth suppressors, resisting the demise of cells, allowing replicative immortality, prompting angiogenesis, and induction of invasion and metastasis (Hanahan & Weinberg, 2011). Two more hallmarks got added a decade later: reprogramming energy metabolism and dodging an immunological response (Fouad & Aanei,

2017). Additionally, there are enabling characteristics thought to cause cancer: mutation, instability of genetic structures, and inflammation caused by tumors. The hallmark of cancer is a tumor, its primary distinguishing feature (Hanahan & Weinberg, 2011). Cancer can be malignant or benign, and all the six initial hallmarks except for invasion and metastasis are indistinctive because they cannot separate cancers that cause harm or are harmless. The relevance of this review is that it provides comprehensive knowledge of stem cells at the cellular level, in contrast to past knowledge. Consequently, stemness facilitates the understanding of stem cells and their microenvironments, and has several reasons why it should get included as a hallmark.

Materials & Methods

Stemness as the New Hallmark of Cancer

For comprehensive and unbiased literature coverage, many sources got analyzed using the literature search technique. Stemness is a keyword that guided the literature search to avoid drifting off-topic. Stemness is the probability of self-renewal or dedifferentiation from the original cell. Remarkably, healthy stem cells can generate all cell types in a mature organism. Cancer cells are found in all hematological and some solid tumors, indicating that stem cells could lead to cancer formation (Malta et al., 2018). Cancer cells are the only common denominator in all types of cells. Stem cells have a long lifespan, and their ability to regenerate and differentiate makes them a hallmark of cancer. Cancer stem cells are resistant to chemotherapy and lead to relapse or metastasis, contributing to poor prognosis in some types of cancer (Malta et al., 2018). In ancient times (300BC), Egyptian scientists cauterized cancer cells using a fire drill (Herdon, 2022). Stemness qualifies as a hallmark because it indicates how healthy stem cells evolve and become cancerous. Essentially, it explains the complexities inherent in neoplastic diseases and the multiphasic development of the pathogenesis of tumors, whereby embryonic cancer cells get traits that make them tumor-causing and eventually malignant. Therefore, stemness explains how stem cells evolve to become a complex system of unique types of cells that interact in a heterotypic manner to form a mass of proliferating cells.

The Differential Degree of Cancer Cells

Cancer cells differ depending on the region from which they evolve. For instance, carcinoma cancer arises from skin exposure to continuous radiation or the surface of glands (Howell & Ramsey, 2019). An example is prostate cancer which results in compact and solid tumors. The cells differ from sarcoma cancer cells in that sarcoma cells originate from connective and supportive tissues like blood vessels and muscles. Leukemia cancer cells arise from the uncontrollable growth of blood cells, while lymphoma cancer cells arise from the white blood vessels' glands. The cells also have varying microenvironments because they arise from different body sections. Thus their surrounding cells and organs differ. The tumor microenvironments also differ significantly because of the different cell types in different body parts. Consequently, tumor microenvironments differ according to the region they exist.

The Interaction of Tumor Cells with their Microenvironment

The tumor cells also interact with the tumor microenvironment in a complex manner. The interaction and the extracellular matrix's properties promote tumor progression (Arcangeli et al., 2014). Tumor cells sense the ECM composition and remodel its properties, thus the hardened nature of the tumor tissue. For instance, tumor cells influence the surrounding cells to utilize

their resources for growth. The tumor cells adopt malignant characteristics to impose their superiority in the microenvironment (Pernot et al., 2022). Adjacent microenvironments exhibit synergy through the interaction of the cellular and non-cellular components. The microenvironments' synergies result in the nourishment of the tumor cells because of surrounding growth elements like hideout from white blood cells' surveillance. Thus, the tumor cells' interact with cells in their microenvironment for their benefit.

The Stem Cell System

Stem cells have unique gene product profiles according to their location in the body. Hence, the unique traits can track stem cells because they behave differently in separate body systems. In select tissues, stem cells are at the top of the chain, which leads to the formation of stem cell systems (SCS) (Aponte & Caicedo, 2017). It means that most organs in the body have a stem cell system. Stem cell systems have basal, transit-amplifying, and differentiation units (Aponte & Caicedo, 2017). The maintenance of stem cells depends on the microenvironment, extracellular matrix, and oxygen levels. Transit-amplifying cells produced by stem cells have a very short lifespan. Notably, they produce daughter cells in preparation for the next stage. Progenitor cells are similar to the parent cells, except they have differentiation markers. In specific situations, the transit-applying cells stop differentiating and become parent cells (Aponte & Caicedo, 2017). Hence, stem cell systems are carefully regulated systems that achieve balance through self-renewal and differentiation to maintain an organ's functions.

When healthy stem cells convert to CSCs, modifications can happen. Notably, there is a possibility that abnormal cell division occurs or epigenetic and genetic changes take place (Afify & Seno, 2019). Hence, the mutation is not the only cause of the formation of cancerous cells. Conversion of stem cells to stem cell systems is the primary cause of most cancers. Immature stem cells are known as embryonic stem cells, and they can cause differentiation in an unidentified phenotype for extended periods (Banyai et al., 2018). Embryonic cells produce progenitors, which control the body's organization of muscles, organs, and skeletons. After the cells have completed their tasks, they are deactivated and leave a colony of stem cells that conduct repairs when needed (Aponte & Caicedo, 2017). The differentiation of a stem cell leads to renewal, and the progenitor formed becomes specialized and conducts the required repair. The renewed stem cell remains in the compartment until it is needed to rejuvenate tissue, and the cycle repeats itself (Menendez & Alarcón, 2014). Thus, stem cells survive for a longer time when compared to healthy cells. Therefore, genetic mutations that can cause a cell to lose control during its self-renewal process lead to the overproduction of stem cells, a condition referred to as cancer.

Reasons for Stemness to be a Hallmark

First, the self-replication feature of stem cells is the primary mechanism behind the nature of cancer disease. Therefore, understanding stemness enhances the knowledge of cancer. A loss in the self-renewal process of stem cells leads to the overproduction of cancer and the formation of cancer stem cells (CSCs). The identification of CSCs was in the 90s by John Dick, who isolated them from acute myeloid leukemia (Moharil et al., 2017). Cancer stem cells are similar to healthy stem cells, except that they only regenerate the cells unique to particular cancer. Stem cells stay dormant until they are triggered to become cancerous (Aponte & Caicedo, 2017). Once the cells are activated, they generate cancers through self-renewal and differentiation into several

types of cells. Cancer cells use the pathways inherent in stem cells to cause uncontrolled self-renewal (Sancho et al., 2016). Secondly, stemness promotes an understanding of the molecular activities of stem cells. For instance, the self-renewal of stem cells gets optimized by genes, and stem cells differ based on their parent tissue (Cai et al., 2012). Understanding the nature of stem cell mutations helps advance chemotherapy because stem cell sequencing eliminates self-replication from the roots. Consequently, stemness should be a hallmark because it promotes an understanding of stem cells' self-replication and helps understand stem cells' molecular activities.

Results

Cancer cells occur from progenitor cells. Adults have more progenitors and can self-renew under particular circumstances (Moharil et al., 2017). Hence, cancer may occur from progenitors because of the large number and ability to self-renew. Differentiated cells also give rise to cancer cells. Notably, the differentiated cells dedifferentiate and become stem cells through oncogenic mutations. The process leads to the self-renewal of the proliferating cells, which leads to a massive cell population in affected tissues that can cause tumors. Therefore, stemness occurs at any part of the life cycle, leading to uncontrolled tumorigenic cell production. Cancer cells also emerge from aged cells undergoing stress during the cell cycle. As the cell ages, mutations collect in the stem cell unit, leading to activation of the oncogene, inactivation of tumor suppressors, and a modification in chromosomes in genes. The chromosomal modifications occur due to genetic mutations like deletion, translocation, and duplication (Sotgia et al., 2019). Reactivated senescent cells produce cancer cells, meaning they do not undergo complete cell cycle arrest. The process leads to hyper-proliferation, catalyzed by telomerase. Cancer stem cells depend entirely on NADH for circulation as 3-D-spheroids (Sotgia et al., 2019). They also indicate stemness markers, such as Oct4, c-Myc, and Nanog (Afify & Seno, 2019). Therefore, incomplete cell dedifferentiation leads to the self-renewal of old cells under stress. The self-renewal gives rise to tumorigenic cells.

Conclusions

The matter of cancer stem cells has existed for centuries. Stemness gets proposed as a new hallmark for cancer. Stem cells can differentiate and form new cells. The Six hallmarks are: maintaining proliferative signaling, evading growth suppressors, resisting the demise of cells, allowing replicative immortality, prompting angiogenesis, and induction of invasion and metastasis. Some characteristics attributed to causing cancer are mutation, instability of genetic structures, and inflammation caused by tumors. The hallmark of cancer is a tumor, its primary distinguishing feature. The literature search methodology entails processing scholarly data sources through screening. Cancer can be malignant or benign. Stemness as a hallmark provides a cellular framework where genetically and phenotypically healthy cells change to a malignant nature. It should enhance cancer treatment because it enhances the sequencing of stem cells. One unresolved question is whether we can use the tumor's microenvironment to fight the uncontrolled replication of stem cells.

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