Cancer stem cells and spatial tumor biology: reconceptualizing oncogenesis and cancer therapy

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■ **Abstract**

Totipotent embryonic cells drive embryogenesis through a trinary model of cell division. Stem cells have the following properties: self-renewal, differentiation into a wide range of cell lines and selective transition to apoptosis/quiescence. Stem cells can transform into cancer stem cells (CSCs) when exposed to environments with persistent unresolved inflammation. Recent studies have discovered that tumors consist of bulk tumor cells as well as subpopulations of CSCs, which show resistance to radiation and chemotherapy and result in tumor relapse and persistence. Recent advances in technology have enabled the study of tumors from the perspective of its spatial organization, leading to the discovery of new molecular topo-biomarkers and topo-regulators, allowing sub-classification of the cell with direct implications in tumor staging and treatment. The highlight in the therapeutic approach to CSCs is the results obtained with hyperthermia. The weakness of CSCs is their sensitivity to hyperthermia in a fever range of 39–42 °C. Furthermore, hyperthermia destroys CSCs resistant to chemotherapy and radiotherapy. This paradigm opens new avenues of research in using Viscum for cancer treatment, specifically within the approach of anthroposophic medicine.

■ **Keywords**

Cancer stem cells (CSCs)
Hyperthermia
Spatial tumor biology
Oncogenesis
Organizational plan

Introduction

Since the introduction of polychemotherapy in the second half of the 20th century, treatments in oncology have advanced considerably. The era of immunotherapy (checkpoint inhibition) has been a major shift in the oncology paradigm, highlighting the role of the patient's own antitumoral immunity and providing new insights about the tumoral microenvironment. Since 2011, check-point inhibitors have achieved important results in advanced tumor response. However, their efficacy and outcomes remain limited with only 25% of patients who receive immunotherapy surviving long-term.

While combined schemes of chemotherapy, target therapies and checkpoint inhibitors are an effective strategy in the control of tumor mass, drug resistance and tumor progression continue to be the main cause of death in cancer patients. Recent advances in cancer research highlight the importance of cancer stem cells (CSCs). These cells are responsible for the initiation, progression, metastatic cascade, and resistance to cancer treatments. CSCs paradigm can introduce new therapeutical approaches achieving more durable remissions. After the immunotherapy paradigm, CSCs are a promising new paradigm in oncology of the 21st century, aided by new technologies such as 3-D culture, liquid biopsy, multi-omics platform, 3-D electronic microscopy and multiplex live-cell imaging. These technologies enable in-depth studies of human tissue samples by visualizing multiple biomarkers simultaneously, allowing the identification and analysis of molecular, spatial and cell phenotypes.

The definition of cancer reflects the epistemological understanding of the times. In 1990, cancer was seen strictly as a genetic disease (1), and by 2006, cancer was defined as a failure of the immune system (2). Currently, cancer can be defined as a disease of CSCs (3). The new technological platforms of today are making it possible to delve deeper into the tumoral biology (4) and thus discover a wide range of highly specific biomarkers that enable tumor sub stratification (5). Following this path of development, oncological diagnostics and treatments are becoming increasingly precise, predictive, and personalized.

Embryonic stem cells

Stem cells are unspecialized cells of the human body. They can differentiate into any cell in the organism and have the ability of self-renewal. Stem cells exist both in embryos and adult cells. Totipotent stem cells can divide and differentiate themselves into the cells of the entire organism.

These cells possess the highest potential for differentiation and give rise to both embryo and extra-embryonic structures, such as the zygote cell and organogenesis. Totipotent stem cells drive embryogenesis following a trinary model of cellular division. These cells generate three types of pluripotent embryonic stem cells, which differentiate themselves and give rise to the following three germ layers: endoderm, mesoderm, and ectoderm. These three germ lines generate the multipotent embryonic stem cells responsible for directing functional organogenesis during embryonic life. Multipotent stem cells continue in extraembryonic life with the capacity to self-renew and differentiate into different cell lineages, to regenerate and repair tissues and worn-out cells of the organism throughout life.

Mesenchymal stem cells (MSCs) are a type of multipotent stem cell that can generate different lineages, including osteoblasts, myocytes, adipocytes, and chondrocytes. MSCs have been widely used for tissue engineering and regenerative medicine due to their immunomodulatory, anti-inflammatory, and angiogenic properties (6).

Hematopoietic stem cells (oligopotent) derived from the mesoderm, can differentiate into myeloid stem cells and lymphoid stem cells. The myeloid series includes basophils, dendritic cells, eosinophils, erythrocytes, macrophages, megakaryocytes, monocytes, neutrophils and platelets. The lymphoid series are B cells, T cells and NK cells. Skeletal muscle stem cells (SMSCs) are unipotent stem cells that can only generate muscle cells. They are also known as satellite cells, as they are located between the plasma membrane and the basal lamina of the muscle fibers. SMSCs are responsible for the growth and repair of skeletal muscle tissue. They fuse with existing muscle fibers or form new ones.

CSCs are a specific type of cancer cell that self-renew and differentiate into multiple progenies with proliferative potential. Selectively they change to an apoptosis/quiescence status. Stem cells maintain the balance between cellular principle and organizational plan of the organism ("Bauplan"). Thus, the number of cells and the cell topos (spatiality) create the architecture of the organs. Advancing in stem cell biology may be the key in clarifying their regenerative role in health and disease.

Cancer stem cells (CSCs)

It has recently been discovered that tumors are composed of the bulk and a subset of CSCs (7). Communication between CSCs and infiltrating immune cell populations in the tumor microenvironment is a new paradigm in understanding tumor immune evasion, metastasis, and recurrence (8). CSCs are resistant to ionizing radiation and chemotherapy and play an important role in tumor progression. Embryonic stem cells can transform into CSCs in environments of persistent unresolved inflammation. They enhance the production of cytokines, chemokines, growth factors, proangiogenic factors and extracellular matrix-modifying enzymes which provide important signal transductions for proliferation and chromosomal instability. Cytokines such as TNF, IL-1, and IL-6 can activate transcription factors ($STAT_3$) to induce a neoplastic transformation of the cell stem quiescent (9). CSCs are a subset of the tumor with increased self-renewal capacity and ability to recapitulate the heterogeneity found in tumors. Antitumor therapies until now have been directed exclusively against the tumor mass. CSCs are refractory to treatments because of their capacity for metabolic reprogramming and can adopt a quiescence phenotype. They also have specific surface markers, CD34, CD38, and CD133 which are specific according to the organ of origin (10) and detectable by liquid biopsy or multiplexing imaging techniques from human tissue samples.

An important characteristic of CSCs is their resistance to anoikis which is the apoptotic cell death occurring when a cell detaches from neighboring cells and the basement membrane. In physiological conditions, when a cell loses its sociological relationship and undergoes cell death by anoikis, the organism does not perceive cells as autonomous entities. Anoikis-resistance allows CSCs to isolate themselves from the tumor focus and to approach the circulation for transport via blood to new metastatic foci, guarded by tumor-derived platelets (TEPs) (11) rendering CSCs invisible to immunosurveillance. This is an active research focus aimed at stopping the metastatic cascade of tumors and to understanding the high frequency of thromboembolic episodes in cancer.

CSCs modulate the tumor microenvironment generating pro-tumor immunity phenotype: tumor-associated M2 macrophages (TAMs), tumor-associated macrophages (TANs), myeloid-derived suppressor cells (MDSCs), Treg lymphocytes, and regulatory and immunosuppressive dendritic cells. The profile of salutogenetic immunity (diurnal) is transformed into a pathogenetic profile in favor of tumor development (nocturnal). CSCs produce exosomes, micro-RNA, growth factors, cytokine cascades, IL-4 and IL-8, expression of PD-L1 (programmed death-ligand 1), Tim-3, production of colony growth factors and TGF-β (transforming growth factor β). CSCs orchestrate the immunity of the tumor microenvironment by forming phenotypes of excluded immunity.

Metabolic phenotypes of CSCs

Metabolic reprogramming of CSCs favor their properties of self-renewal, multipotentiality, DNA self-repair, radio resistance, chemo resistance, invasiveness and metastatic capacity (12). CSCs have different phenotypes and are on the one hand hypoxic versus normoxic, on the other hand quiescent versus proliferative. The metabolic demands of CSCs vary based on their distinct phenotypes. CSCs have fewer and less mature mitochon-

dria resulting in reduced reactive oxygen species (ROS) levels, needed to maintain quiescence and the self-renewal phenotype. CSCs have high metabolic plasticity and adaptability following micro-environmental fluctuations. CSCs can reprogram metabolically in three different phenotypes (13).

1. *Combined phenotype:* In normoxic conditions the glycolytic pathway and the oxidative phosphorylation pathway (OXPHOS) are activated, increasing mitochondrial mass and fatty acid oxidation (FAO). The combined phenotype increases the proliferative and metastatic capacity of CSCs.
2. *Oxphos phenotype:* In the nutrient deprivation phase, glycolysis is reduced while oxphos and mitochondrial mass increases. This metabolic reprogramming phenotype, together with the acquisition of quiescence, confers to CSCs resistance to oncological treatments.
3. *Glycolytic phenotype:* Under hypoxia conditions, they increase glycolysis, reduce oxidative phosphorylation acquiring a proliferative profile.

Metabolic reprogramming of CSCs allows the reverse of the Warburg effect of the standard cancer cell, in the presence of oxygen activating the glycolytic pathway instead of OXPHOS. CSCs acquire quiescent status, decreased proliferation, low metabolic activity, decreased pharmacokinetics and facilitate chemo-radioresistance.

Tumor spatial biology

Although modern biology and medicine have been dominated by molecular paradigms (genetics and biochemistry) for the past century, recent works from transversal fields have revealed that supramolecular events play an important role in cell and tissue development. The emergence of this new spatial biology field has garnered interest in oncology. The most fundamental questions in this field are how tumoral cells spatially organize themselves and what their meaning is in tumor biology. Recent studies of tumors from the perspective of spatial organization have uncovered new topo-biomarkers and topo-regulators associated with tumor growth, metastasis, and drug resistance. Topo-biomarkers are new prognostic factors and will be considered as substage criteria soon. High multiplexed fluorescence microscopical images explore cancer biology with high resolution *in situ*. These new technological platforms combine technology of single-cell and spatial analysis powered by high techno platforms with multi-omics data integration in a precise and fast workflow (14). The word "spatial" in biology describes how molecular and cellular entities relate to each other in relation to their relative positions in a tissue. Spatial biology analyzes individual cells in the context of their 3-D environment and explores the spatial signatures of a tumor.

The 3-D tumor environment includes cell sociology, the extracellular matrix, spatial configuration (architecture) of a tissue or organ and tumor microenvironment. In addition, the 3-D spatial environment allows defining the spatial-temporal situation for the expression of different molecular patterns in individual cells (subclones), depending on their spatial location and interactions with the environment.

The spatial study of the tumor with integration of multi-omics platforms allows the establishment of the new tumor subclassification parameters, allowing individualized signatures with direct implications in precision diagnostics and treatment. In the human organism, two-dimensional entities do not exist. Every cellular and molecular entity assumes a 3-D conformational pattern. Cells do not exist as isolated entities. They are sociological entities that form three-dimensional structures ordered according to the organizational plan of the organism ("Bauplan").

The extracellular matrix (ECM) underlies the three-dimensional cellular organization. Plasticity, integrity and density of the ECM and the tensile forces act on it, influencing cell biology in health and disease (15). Until 1990, two-dimensional monolayer models were used in the culture of cancer cells. 2-D cultures are inefficient for the study of processes associated with cellular response to ionizing radiation or chemotherapy. 3-D cell culture allows the study of morphology, proliferation rate, differentiation, interactions with the extracellular and immune microenvironment. In addition, 3-D cultures mimic conditions *in vivo* and may provide an alternative to animal models.

Tumors have complex systems with varying degrees of genomic and spatial heterogeneity. The spatial organization of the tumor is a determining factor of intra- and intertumoral heterogeneity, directly linked with diverse clinical presentations. This heterogeneity is strongly associated with therapeutic resistance and continuous relapses. Differentiated tumor areas can be established. These are spatially related with specific phenotypes that interact with the tumor microenvironment. The location of cell groups in the intratumoral space is a key to understanding biological profiles. The spatial patterns which order the organism follow laws of fractal geometry (16).

Tumors are spatial unorganized entities which combine cancer cells, immune cells, CSCs, extracellular matrix, and healthy cells. Spatial biology reveals a new complexity of the tumor with different architectural contexts and determined locations that have direct implications on tumor evolution and prognosis (17). Individual cancer cells may behave biologically different depending on their spatial location and interactions with adjacent cells. A high degree of inter- and intratumoral heterogeneity is associated with a poor prognosis, often leading to fatal outcomes. Spatial tumor subclones determine the efficacy of therapeutics. Some treatments can trigger resistance and immune escape by selective pressure on the tumor microenvironment, favoring the persistence of CSCs and a spatial rearrangement of resistant subclones (18).

Spatial organization consists of supramolecular elements that order and organize molecular and cellular patterns. The loss of spatial ordering is the supramolecular origin of neoplastic transformation, preceding the activation of intracellular molecular and oncogenetic processes.

The immune context of the tumor comprises the density, composition and spatial organization of molecular and cellular entities that provide relevant information on the prediction of response to treatment and prognosis of the patient. Spatial patterns constitute an integral part of the viability of the tumor subclones that compose the new tumoral organ. This allows us to affirm that the parameters of localization and interaction of cellular subclones serve as topo-biomarkers and allow correlating responses to treatment and clinical outcomes.

Cancer growth and progression are spatial processes involving the disruption of the organizational plan of the organism ("Bauplan"). Therefore, spatial patterns in cancer are nowadays an integral part of oncology and allow the implementation of a new tumor classification and staging based on new lines of tumor sub-stratification with greater precision, response prediction and therapeutic individualization. The spatial biology of cancer opens new questions and very promising research frontiers. How do tumor subclones grow and reorganize spatially? How can chemo- and radiotherapy-induced pressure influence them? What is the role of tumoral spatial subclones at different stages of tumor genesis? How do they evolve in CSCs in the tumor space? What do the spatial signatures in immune escape mean?

Inter- and intratumoral spatiality is very dynamic. Hotspots, cold moles, immunosensitive and immune deserted landscapes are formed. Interaction with the tumor's microenvironment modifies tumor sub-clonality at the primary site and at metastatic sites. It is important to know how subclones interact spatially with each other and with their tumor microenvironment. Spatial biology introduces new lines of knowledge in current oncology highlighting the significance of supramolecular factors in the origin and evolution of cancer. Based on these new insights in tumor biology, the concept of oncogenesis is reconceptualized from morphogenetic and spatial principles (supramolecular), aligning with ideas proposed a century ago by the founder of anthroposophical medicine.

Until now, the study of oncogenesis has primarily focused on molecular factors such as genetics and biochemistry. However, in anthroposophic medicine, the concept of space and form plays a crucial role in understanding the process of morphogenesis during both the embryonal and postembryonal periods. This broader perspective on the human being is essential for comprehending health and disease. By drawing insights from anthroposophic medicine and observing morphogenesis in nature, it becomes evident that morphogenesis follows the principles of non-Euclidean geometry, reflecting the forces of levity (19). Within this framework, self-similarity emerges as an important principle in the evolutionary process of the organic world. Similarly, in humans, organogenesis is guided by these same formative laws. In contrast, oncogenesis represents a disruptive spatial tendency that leads to a loss of self-similarity and coherence.

CSCs and therapeutics

Currently, multiple lines of research are focused on developing therapeutics against CSCs. Controlling CSCs is crucial for managing tumor progression and overcoming treatment resistance. The oncology research community is currently tackling the challenge of targeting CSCs, with the help of advanced techniques such as 3-D cell culture, 3-D electron microscopy, and multiplexing technologies. Among these approaches, hyperthermia (HT) has shown promising results. CSCs are particularly sensitive to hyperthermia within the fever range of 39–42 °C, making it a significant finding in this field (20). HT combines with radiotherapy, chemotherapy, and antibody-targeting to improve CSC-selective elimination. One such approach is Nano-HT, which involves intratumoral implantation of magnetic nanoparticles like iron oxide, gold-silica, nanoshells, and carbon nanotubes. These nanoparticles can be released when subjected to a heat source (21). However, the potential results arising from the combination of these innovative therapeutic approaches with HT remain largely unexplored.

HT produces important biologic effects within normal and tumor tissues:

- HT causes membrane dysfunction to contribute to cell death, affecting permeability of cellular membranes (including mitochondrial membranes), changes transmembrane transport proteins, ion channels, cell surface receptors, and signal transduction points. Furthermore, HT causes denaturation of nucleic acid proteins.
- HT induces necrosis and apoptosis. This type of cell death does not generate DAMPS (damage-associated molecular pattern) unlike death by necrosis. HT can increase the production of reactive oxygen species (ROS) that facilitate apoptosis.
- HT improves intratumoral oxygenation, increases perfusion within tissues and modifies local pH.
- HT increases tumor immunity: releases intracell RNA, DNA, and immunogenic proteins, activates dendritic cells and macrophages, and increases local and specifics anti-tumoral immune responses.
- Heat shock proteins (HSP) are released by heat and activate dendritic cells, tumor-infiltrating T-lymphocytes.
- HT induces tumoral exosome liberation loads with proinflammatory cytokines that increase serum levels of IL-6, IL-8 and TNF-α.
- HT kills tumor cells independent of the cell cycle status. CSCs in quiescent status (chemo and radio resistance) are destroyed by HT and exposing CSC-specific antigens to dendritic cells and increase immune intratumoral cells (22).

CSCs, warmth and space

The role of warmth and thermoregulation in living organisms and how it relates to health and disease is currently unknown. In anthroposophic medicine, fever is seen as a manifestation of the organism's ability to maintain health and self-similarity. Acute febrile inflammation triggers regulatory thermogenesis and a salutogenic immune response. This rapid and responsive behavior is essential for maintaining the biological integrity of the organism and for distinguishing between what belongs to the organism (self) and what does not (non-self).

Chronic non-febrile reactivity increases the risk of a protumoral condition, which is caused by an imbalance between the organizational plan of the organism ("Bauplan") and the cellular principle. This imbalance leads to the development of a cancerous landscape. The predominance of the cellular principal results in fragmentation, heterogeneity, fibrosis, and progressive cooling, establishing a protumoral immunity known as nocturnal immunity. Within this immune context, CSCs drive the process of disruptive neo-organogenesis (23). From an anthroposophic perspective, CSCs are characterized as disruptive germ cells that retain etheric properties not influenced by the human organism (self). Specifically, during their formation, CSCs lose their proper connection with the suprasensible levels of human beings. They represent disruptive germinal points that are unable to guide the cell principle. According to R. Steiner, the "revolution of physical forces against the forces of the etheric body" (24) occurs in specific points, creating optimal conditions for the formation of CSCs. The formation of CSCs is considered the initial step in tumoral neo-organogenesis. These cancer stem cells in the ability to isolate themselves from the surrounding cellular environment through a mechanism called "anoikis resistance". Instead of being regulated by the suprasensible organization, these CSCs seek outgrowth niches to proliferate, resulting in the formation of disruptive cell lines with varying clonal dispersion.

The physical stresses exerted on the organ induce the spatial arrangement of the extracellular matrix, whereby a distortion of the fractal anatomy influences the stage for oncogenesis. During the precancerous phase, the stressed extracellular matrix reshapes the functional anatomy of the organ. In liver cancer and breast cancer, fibrosis precedes the neoplastic transformation. In anthroposophic medicine, founded one century ago, the concepts of space and form are key macroscopic factors for understanding organogenesis and explaining oncogenesis. Currently, we observe a convergence of models and recent studies that are based on relevant macroscopic aspects for the diagnosis and prognosis of cancers. There are research lines focusing on detecting modifications in the fractal architecture of organs as early diagnostic biomarkers in breast cancer. In the case of lung cancer, areas of resistance to chemotherapy exhibit a more significant loss of fractality (25, 26).

CSCs and Viscum album

In contemporary scientific research we can identify points of convergence with the research initiated by anthroposophic medicine. The founder of anthroposophic medicine pointed out the importance of fever as a salutogenetic process and the absence of a fever reaction as a facilitator of tumor genesis. The Viscum album treatment has two important therapeutic objectives in oncology: promoting the patient's healthy body warmth (endogenous continuous hyperthermia) and facilitating spatial reorganization of the organism through self-similarity and coherence.

In integrative oncology, Viscum album therapy can be viewed as a progressive and continuous form of endogenous hyperthermia. Its goal is to restore thermoregulation and recover the acute febrile inflammatory response. Treatments involving high doses (1000 mg) of Viscum album administered intravenously periodically can induce hyperthermia within the febrile range with manageable safety profiles (27). Continued endogenous hyperthermia induced by Viscum album in the febrile range may promote the biological inviability of CSCs. This may help explain the long-lasting remissions reported in medical literature for Viscum therapy (28, 29, 30).

The paradigm of CSCs and tumor spatial biology opens new challenges for Viscum album research:

1. Studies of Viscum album in 3-D tumor cultures and their role in the spatial reorganization of cancer subclones and the tumoral niche.
2. The impact of Viscum album on tumor spatial reorganization as a prognostic and treatment response factor.
3. Future position of hyperthermia combined with intravenous Viscum album perfusion in pre/post operative treatment for locally advanced cancer.
4. Impact of Viscum album given intravenously plus externally applied hyperthermia on CSCs markers CD34, CD38, and CD133 and circulating tumor DNA (ctDNA) detected by liquid biopsy. The liquid biopsy precedes the clinical detection of the tumor by 4 to 6 years.

The new paradigm of space tumor biology and CSCs is profoundly modifying the conceptualization of the oncogenesis and promises new therapeutic contributions to cancer treatment. After 100 years, Viscum therapy has found converging paradigms, providing the opportunity to participate in cutting-edge cancer research at the highest level.

From the perspective of integrative oncology expanded by anthroposophy, we can identify four fundamental lines of cancer treatment:

1. To remove the bulk tumor (immunotherapy, targeted therapy, surgery, radiation, and chemotherapy) and eliminate the CSCs (cancer stem cells), for example, by using hyperthermia combined with Viscum therapy and checkpoint inhibitors.
2. To restore the lost architecture in the tumor site.

3. To restore a healthy body temperature (36.5 °C average) and restore the ability to respond to fever-induced hyperthermia.

Viscum album has traditionally played an important role in anthroposophic cancer therapy. In the future, this special role could also gain in value in the context of modern cutting-edge science.

Conflict of interest

The author declares no conflict of interest.

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