Exploring the Role of Stem Cells in Cancer Development and Progression

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Abstract

Tumors comprise two types of non-cancerous cells, first recruited cells such as stem cells and macrophages, and second, tissue-steady cells that are part of the tissue including adipose cells, fibroblasts, and steady macrophage-derived cells, all having a significant impact on tumor progression. This review addresses some effects of stem cells on cancer advancement as the predominant outcome of stem cell therapy on cancer cell lines revealed controversial results. In addition, this review will address some reasons of distinct cancer responses and hypothesizes the notion of unfolded protein response as a key switch in cancer development.

Keywords: Cancer progression; Stem cell; Fused cell; unfolded protein response

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Introduction

Stem cells are involved in a variety of processes in the body, and their uncertain functions in cancer microenvironment are still an open challenge. In the body, some cells are a steady stay at the organ, for example, macrophage-derived cells such as dust cells in the lung tissue, brain microglia, and more importantly, stem cells. Tissue-specific stem cells ubiquitously serve in approximately every tissue; however, in case of wound healing and cancer progression, stem cell recruitment is the most exciting interpret. The question is why the tissue that has already its own stem cells with tremendous proliferation capacity still recruits from other parts of the body. Stem cells show a variety of functions during cancer, serving in some oncogenic disorders as suppressors, for example in breast cancer and melanoma but having an intriguing function in the majority of tumors. Stem cells produce a variety of interleukins (ILs) and growth factors and are capable of influencing cancer metabolic pathways. Stem cell microvesicles (MVs) or nanovesicles (NVs) have a critical impact on bystander cells (Fig. 1). Regarding the vesicles, for example, several studies revealed promising approaches for multiple sclerosis; even it has walked through drug discovery. Despite prominent achievements, there are controversial scope in some area including the duration of having stable MVs/NVs derived from mesenchymal stem cells (MSCs). Regarding direct MSC transplantation, high risks are remaining considering an influence on extracellular matrix (ECM) manipulation that may activate tumorigenesis. A promising strategy may be the transplantation of endothelial progenitor cells (EPCs) that may be more effective than MSCs; EPCs can be isolated from the bone marrow and are circulating in the body, although at rare levels in aged people. Nonetheless, there is only one clinical trial demonstrated its benefits in brain damage. Application of MSC medium (MSCM) helped to keep chondrogenic features and push forward cell proliferation in cartilage disorders, cardiac cell treatment, and cancer reduction. Nevertheless, in some cancer cell lines, MSCM had detrimental effects. Stem cells are not the only cells with exosome transmission capability. Adipose cells can also influence distant tissues via exosome transmission. This review will discuss the role of stem cells in malignancy ignition, support, and will hypothesizes the notion of unfolded protein response as a coordinator switch in cancer semi-differentiation trajectory as cancer cell show a variety of differentiated cells hallmarks during progression.
Fused stem cells

A recent study showed that MSCs could fuse with other cells to generate hybrid cells. When using MSCs from a male recipient and co-culturing them with breast cancer cells from a female donor, the chromosome Y was deleted from some of the formed hybrid cells after a few passages while such hybrid cells displayed a significant migration potential, resistance, and proliferation, yet without whole two sets of chromosomes\(^1\). Likewise, evidence revealed that MSCs could generate cancer in prostate tissue by fusing with normal cells\(^2\). Such hybridization may be one of the reasons for cancer triggering, and some questions like whether MSCs migrate toward tumor place or impose cancerization remain open. This feature does not occur only in a laboratory environment between MSC and cancer cells but also in polyploid giant cancer cells (PGCCs) frequently happen\(^3\). While polyploidy has been seen as a defective phenomenon, there are natural cells that undergo such event like muscle cells and hepatocytes. Cancer stem-like cells are a result of epithelial-mesenchymal transition (EMT). These sorts of cells acquire stem cell abilities like migration and adhesion-independent growth and are not involved in cancers but act during wound healing process and are rather epithelial-like or mesenchymal-like cells\(^4\). Expression of reprogramming transcription factors including NANOG, SOX2, and OCT4 is a common feature among MSCs, PGCCs, and EMT cells that come off significant chemotherapeutic resistance.

Coordination of cancer metabolism by MSCs

Cancer-associated fibroblasts (CAFs) are cells that invade tumors strictly, having a significant impact on cancer metabolism that defines specific phenotypes in tumor and bystander cells (Fig. 1). Tumor subtypes and their non-cancerous cells communicate with metabolic pathways via paracrine agents by pyruvate, lactate, and \(\alpha\)-ketoglutarate\(^5\), with a causative relationship with cell migration upon expression of integrin, fibronectin, and other migration-related proteins. Studies revealed that CAFs cells can be derived from MSCs; literally they are transformed from fibroblasts and also it can induce CAF genetic phenotypes alteration when a mutant fibroblast (CAF cell) exposed to normal fibroblast\(^6\). Cancer cell niche is an important side of cancerization, instance; metabolic agents are directed by pyruvate and \(\alpha\)-ketoglutarate that aid collagen hydroxylate activation via collagen prolyl-4-hydroxylase (P4HA), an important process of collagen remodeling implicated in the formation of a metastatic niche\(^7\) controlled by bystander cells. Apparently, tumor cells impose normal cells to assist in specific scaffold fabrication which has unique quality, to illustrate, in a recent state of the art study reported that decellularized ECM isolated from human colorectal tumors stimulated macrophages to express a relatively anti-inflammatory phenotype with increased expression of IL-10 and the transforming growth factor-beta (TGF-\(\beta\))\(^8\).

Stem cells growth factors and interleukins

MSCs release a large panel of cytokines such as IL-1\(\beta\), IL-6, IL-8, IL-10, IL-11, IL-12, IL-14, IL-15 and growth factors such as the stem cell factor, hepatocyte growth factor, or vascular endothelial growth factor\(^9\). The role of MSCs in tumor formation is still controversial, including tumor-promoting and tumor-suppressing effects. It is believed that the influence of MSCs on can-

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**Fig. 1** Tumors comprise several non-cancerous and cancerous cells acting in concert, with a particular impact of MSCs on cancer cells via the cell secretoome, the production of microvesicles (MVs) and nanovesicles (NVs), and/or exchanges via tight junctions.
cancer cells (including immune suppression) may be mediated via cell secrtope (immune-effective ILs and their signalization cascades) and exosomes in which contain miRNAs and/or mitochondria or via tight junctions between cells\(^\text{[3]}\). For instance, IL-1β has critical results on all three mitogen-activated protein kinase (MAPK) and nuclear factor kappa B (NF-κB) activation\(^\text{[2]}\) that have suppressor effects in the early stages of cancers, although some activating roles on advanced cancers have been also reported\(^\text{[3]}\), the same features being described for TGF-β\(^\text{[26]}\) and for IL-8 via extracellular-signal-regulated kinase (ERK) signaling\(^\text{[27]}\). Also, IL-1β, IL-6, and the vascular cell adhesion molecule 1 (VCAM-1) aid circulating tumor cells to cluster with neutrophils\(^\text{[28]}\). In addition, pro-inflammatory cytokines can up-regulate the intercellular adhesion molecule 1 and VCAM-1 expression on MSCs to attach to T cells\(^\text{[29]}\). It is also shown that IL-22 mediates DNA damage response in intestinal epithelial stem cells. Indeed, these molecules are aware of stem cells to identify DNA damages and repair them faster; however, IL-22 also identified as a cancer-promoting cytokine\(^\text{[30]}\). MSCs have close interplays with macrophages; Pro-inflammatory M1 macrophages undergo tryptophan depletion upon MSC cytokine mediators via interferon-gamma (IFN-γ) and prostaglandin E2 secretion and vice versa M1 macrophage recruit MSCs via IFN-γ, monocyte chemoattractant protein 1, and IL-8\(^\text{[30]}\). Of final note, MSC exosomes have shown to activate VEGF expression via ERK1/2 cascades\(^\text{[31]}\).

**Tunneling nanotubes (TnTs)**

The idea of organelle exchange has attracted broad attention, leading to the discovery that cells tend to share their cytoplasmics via tunneling nanotubes (TnTs) that leads to cytoplasm and mitochondria exchange\(^\text{[32]}\). The concept of mitochondria transition is based on the (still controversial) idea that the recipient cell will undergo a modulation of the phenotype (including energy profiles). Mitochondria exchanges may most importantly occur between MSCs and cancer cells, making cancer cells chemoresistant\(^\text{[33]}\). Of interest, MSCs have been reported to undergo active proliferation when given mitochondria from muscle tissues\(^\text{[34]}\). Besides, TnTs, mitochondria transfer may occur by cell fusion, microvesicles, gap junctions, and direct mitochondria uptake (Fig. 2). Mitochondria are the central part of consuming and cell energy and many cancer drugs are intervene with mitochondria directly or indirectly\(^\text{[31]}\). Mitochondrial dysfunction is one of the cancer attributes, and its consequences on cell development, metastasis, and motility have been the focus of numerous studies\(^\text{[35]-[38]}\). Recently, it is shown that mitochondria could impose EMT in cancer cells by extracellular regulatory factors\(^\text{[39, 40]}\). Such phenomena may be orchestrated by fumarate or anti-metastatic miRNA results in epigenetic methylation\(^\text{[6]}\). Interestingly, mitochondria depletion leads to TGF-β overexpression that also controls EMT\(^\text{[40]}\).

**Mesenchymal Stem Cells support Cancer by UPR response**

Tumor and its surrounding cells have enjoyed comprehensive studies so far\(^\text{[3, 41, 44]}\). However, current study intended to introduce a new theory for MSC function on cancer surrounding by UPR linkage. Theory overview; UPR stress implicates into a range of cell developing phenomenon, and it has been frequently interpreted as the main reason for several evolutionary processes from Drosophila to Mammalian\(^\text{[45-47]}\). UPR response is in charge of numerous cell response and profound of signal transition pathways namely, MAPK\(^\text{[47]}\) and NF-κB\(^\text{[44]}\) are sort of UPR companion.

Classical UPR response perspective issues down-regulation of most genes due to phosphorylated eIF2α, this will ubiquitously attenuate translation initiation and shows a huge impair on the spectrum of genes expression\(^\text{[49]}\). However, a recent study showed that when UPR responses start stem cells lose stemness markers and they get into a differentiated state, probable reason for this alteration is phosphorylated eIF2α causes swift loss of short-lived proteins such as c-MYC that is a crucial player in stem cell fate. Interestingly, they addressed the amount of Endoplasmic Reticulum (ER) and mitochondria enhancement in the cells which have not met UPR stress (interestingly amount of ER and mitochondria in stem cells are remarkably significant, it seems this is part of intact UPR response quality cells)\(^\text{[38]}\). MSCs co-cultures show enigmatic features, for instance, coculture of MSCs with meniscus cells caused increased hypertrophic differentiation, which is sort of a bone like-marker\(^\text{[41]}\). This sort of cell-cell interaction is not merely MSCs quality also bone marrow adipose (BMA) cells
Reprogramming genes exhibit significant rewiring potential and are in charge of a range of gene regulation. This flow chart tracks the causative trend of some indicators; cytokines enormously effect signal transition pathways such as MAPKs, NF–κB, and so on. These pathways ended with UPR response and pursue by reprogramming genes. Another important way of cancer progression works out by metabolism intermediates such as pyruvate, lactate, etc. these substances can influence on UPR response and even directly on reprogramming genes. There is a novel element which is nanotube’s enigmatic material, especially mitochondria i.e. it can directly manipulate reprogramming genes. Fused cells are a novel way of cancer advent and progression; it leads to aneuploidy and also makes giant cells. This sort of cell can produce several cytokines and show a high potential of putting up with situations.

show the same impression on stem cells. This interplay is considered as lipotoxicity of fatty acids (FA) to osteoblasts.

This paper argues that cancer cells need to have fragile UPR response to instigators to put up with situations because UPR maybe is the only pathway with revolutionary ramification. UPR major researcher professor Afshin Samali says, “in cancer cells, UPR is already activated at basal levels, whereas in most cells UPR and other stress response pathways are only activated when there is a loss of protein homeostasis (proteostasis).” To illustrate, plasma cell differentiation leads to manipulated UPR response; regard to this, some UPR elements get susceptible, including ER chaperones such as BiP, GRP94, and ERdj3, while others like CHOP and a target of the PERK branch of the UPR get blunt. One reason for the PERK feature is activation of the PERK branch will make a universal suppression of protein synthesis and this is contrary to plasma cell duty, which is producing vast quantities of protein.

Conclusion

Non-cancerous cells, especially MSCs, influence cancer progression via tumor microenvironment crosstalk, where cancer cells adapt their milieu to take advantage of the host physiology and condition. It seems MSCs navigate cancer cells into EMT by different facilities such as mitochondria, hinting UPR response, cytokines and so on. Nevertheless, such potential of MSCs in a tumorigenic situation is still controversial and need to be elucidated by more experimental work in clinically relevant setups.

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