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Research paper

Immune modulation by a cellular network of mesenchymal stem cells and breast cancer cell subsets: Implication for cancer therapy

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ABSTRACT

The immune modulatory properties of mesenchymal stem cells (MSCs) are mostly controlled by the particular microenvironment. Cancer stem cells (CSCs), which can initiate a clinical tumor, have been the subject of intense research. This review article discusses investigative studies of the roles of MSCs on cancer biology including on CSCs, and the potential as drug delivery to tumors. An understanding of how MSCs behave in the tumor microenvironment to facilitate the survival of tumor cells would be crucial to identify drug targets. More importantly, since CSCs survive for decades in dormancy for later resurgence, studies are presented to show how MSCs could be involved in maintaining dormancy. Although the mechanism by which CSCs survive is complex, this article focus on the cellular involvement of MSCs with regard to immune responses. We discuss the immunomodulatory mechanisms of MSC-CSC interaction in the context of therapeutic outcomes in oncology. We also discuss immunotherapy as a potential to circumventing this immune modulation.

1. Introduction

In the mid-20th century, scientists noted that culturing bone marrow and spleen cells grew colonies of fibroblastic phenotype, leading to the concept that precursors of fibroblasts exist and were termed colony forming unit-fibroblasts (CFU-F) [1,2]. These cells were later designated as mesenchymal stroma/stem cells (MSCs). MSCs have undergone extensive studies, which provide in-depth insight into the growth and maintenance of organ-specific tissues, along with insight into how they regulate immune functions within an inflammatory milieu.

The information gained in studying MSCs has led to therapeutic potential for these cells, including involvement in cellular delivery of drugs and as immune modulators. As multipotent cells that can self-renew and differentiate along distinct lineages, MSCs can also regulate immune responses [3]. The immune biology of MSCs is not mutually exclusive of the growing literature on cancer stem cells (CSCs), which are a subgroup of cancer cells with stem cell-like and tumor initiating properties.

A common function between MSCs and CSCs is their ability to interact with immune cells to modulate the immune system. Through an interplay between surrounding cells and factors in the microenvironment, stem cells can in many cases suppress the immune system, while in others enhance [4]. These interactions are important when discussing tumorigenesis as this is comprised of a complex system of signaling influenced by these cells. By discussing the immune effects of each type of stem cell individually as well as their interrelationship, we can begin to develop a discussion on navigating this interplay of immune modulation to enhance cancer therapies.

2. Mesenchymal stem cells and immune modulation

Since their discovery, MSCs have demonstrated the potential to differentiate into cells of a differentiate milieu, an affinity for migration to site of injury and tumor, easy maintenance *in vitro*, and a crucial role in tissue regeneration and immunomodulatory function [3,5]. These properties of MSCs have allowed for their safe use in clinical applications and the subject of a plethora of clinical trials.

MSCs are one of the many stem cells that reside in the bone marrow. These cells play a fundamental role in monitoring afferent and efferent blood flow in the bone marrow and are thus often referred to as 'the gate keepers' of the bone marrow. Studies have shown that MSCs possess potent immunosuppressive capacity via soluble factors, insoluble factors, and cell-to-cell interaction [5–7]. In addition, studies have shown that MSCs can reduce inflammation *in vivo* [7]. Further proof of the immunosuppressive effects of MSCs has been shown when *in vivo* depletion of a specific tumor stromal cell population restored native antitumor activity [8] MSCs not only reside in the bone marrow but on or in many other vascular sites in the body which allows for easy metastasis to site of injury [5,9].

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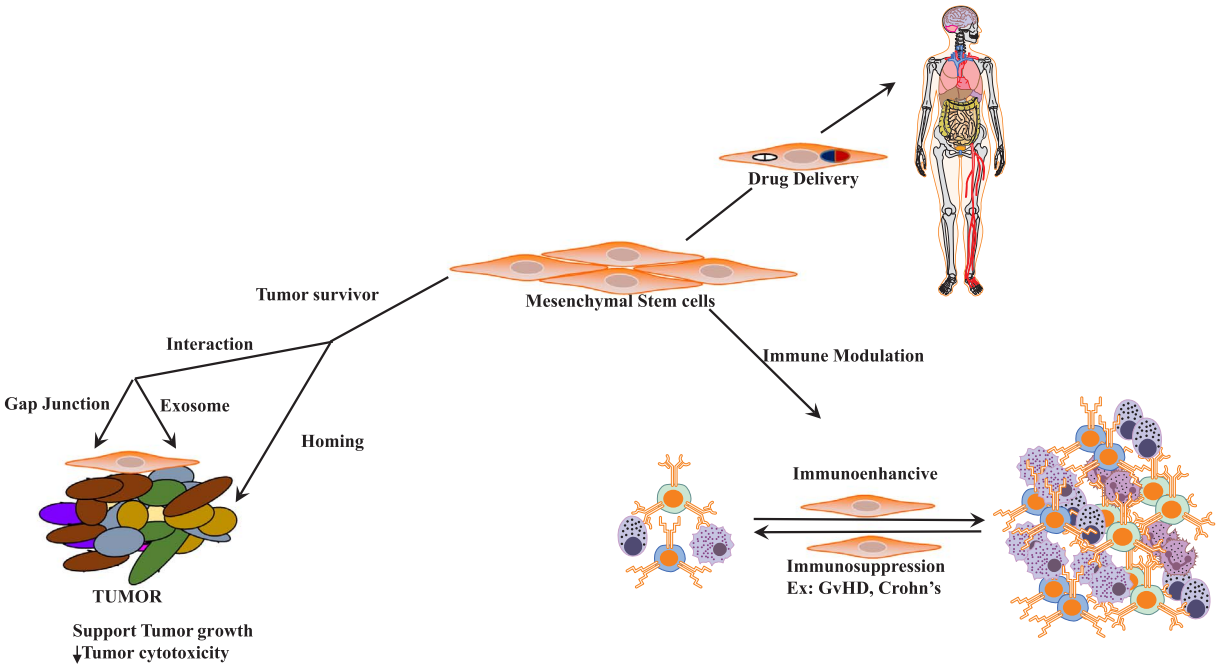

Fig. 1. Multiple roles of MSCs. Shown at left are the mechanisms by which MSCs facilitate tumor survival and dormancy. The right section of the diagram shows MSCs as cellular drug delivery and their ability to modulate the immune system.

MSCs can either be immune-suppressive or immune-enhancive to cancer cells (Fig. 1) [10]. Upon encountering an immune insult such as cancer activated MSCs have demonstrated the ability to sense microenvironment changes via paracrine molecules which allow docking at the site of injury and the release of therapeutic molecules. Studies indicate that upon homing to the tumor site MSCs release mediators that are detrimental to tumor progression [11]. The source of MSCs can be indicative of the role MSCs play on the tumor. MSCs can be found in many other tissues besides the bone marrow such as umbilical cord blood adipose tissue, amniotic fluid and the placenta. One study demonstrated that adipose-derived stem cells (ADSC) show homing capacity potential to glioma [12]. Thus the difference in phenotype based on the source of MSC can dictate metastatic and homing potential.

3. MSCs and drug delivery

This article focuses mostly on the immune suppressive properties of MSCs. However, it is worth noting that MSCs are also multipotent cells with functions similar to stem cells. MSCs show functional plasticity and can respond to tissue insult [13]. These functions provide the MSCs with the ability to navigate organs, including the lymphoid system. Despite MSCs being non-hematological immune cells, they can be given as off-the-shelf cells [14]. This property of MSCs makes these cells attractive for drug delivery [15].

As off-the-shelf method of delivery, this implies that MSCs are able to cross allogeneic barriers. Due to the expression of receptors for chemokines, MSCs can home to sites of tissue injury such as inflammatory sites where the mediators can license them to become immune suppressor cells [13,16–23]. Thus, the MSCs will not be rejected or cleared by the immune system. This will provide the MSCs with a window of opportunity to deliver the desired drug. Also, the prolongation of MSCs in a foreign host might not be an advantage since the MSCs are from an allogeneic host. Since they are multipotent cells, if the environment is permissive, the MSCs could expand at the target site through self-renewal [24]. This will allow the MSCs to deliver the drug for a prolonged period. However, this might not be a desirable outcome since the drugs might not move to the daughter cells. Also, this ability enables improved survivability once at the target site, increasing drug delivery efficacy.

Currently, the method by which MSCs can deliver the drugs is under experimental investigation. There are several strategies currently being investigated to deliver anti-tumor cargo. The methods capitalize on the plasticity of MSCs such as survival in foreign hosts, the ability to form gap junctional intercellular interaction with other cells, expression of cytokine receptors, and response to the microenvironment. The secretome of MSCs has been implicated in the therapeutic effects of MSCs. The loaded cargo can easily be excreted by the cell and directly delivered to the target tumor tissue [25–35]. Based on the discussion in this section, MSCs exert properties that can allow them to deliver anticancer agents directly to tumors. Besides delivering drugs, MSCs can also be used as a delivery system to shuttle small non-coding RNA to tumors. Researchers have demonstrated a non-toxic approach with the use of MSCs to deliver antagomiR-222/223 to dormant breast cancer cell [35]. Similarly, other studies used MSCs to deliver anti-cancer agents via adeno/retroviral vectors, oncolytic viruses or drug loaded polymeric nanoparticles expressing tumor suppressing agents to tumor sites [10,36]. Constructs utilizing gene-directed enzyme prodrug therapy, delivery of pro-apoptotic proteins, and exosome-based cargo delivery will be discussed in more detail in the following sections.

3.1. Gene-directed enzyme prodrug therapy

MSC-based gene-directed enzyme prodrug therapy (GDEPT) or "suicide gene therapy" is designed around the use of MSCs as a pharmacologic pump. A viral vector that encodes a gene for a prodrug-activating enzyme transgene is incorporated into MSCs where the vector is transcribed and translated into the desired enzyme within the target cell. Transduced MSCs are then reinjected and allowed to home to the tumor site at which point the prodrug is administered. The cytotoxic metabolites that are produced within transduced MSCs are then pumped out into the local microenvironment killing neighboring tumor cells by a 'bystander effect' [15,37–39]. Herpes simplex virus thymidine kinase (HSV-TK) with Ganciclovir (GCV) and *E. coli* cytosine deaminase (CD) with 5-fluorocytosine (5-FC) are commonly used suicide gene constructs. Incorporation of a suicide gene enables efficient elimination of transduced MSCs lowering the risk of malignant transformation. Also