

# Do Cancer Stem Cells have an Immunomodulatory Role Different from the Bulk of Tumor Cells?

# Hazem Ghebeh\* and Monther Al-Alwan

Stem Cell & Tissue Re-engineering Program, King Faisal Specialist Hospital and Research Centre, Saudi Arabia

## Abstract

Cancer is one of the leading causes of death worldwide. In normal settings, the immune system is responsible for clearing cancer cells from our body. However, many patients develop immune tolerance to tumor cells through up-regulation of immune regulatory molecules, release of immune suppressive factors in the tumor microenvironment and/or recruitment of regulatory/suppressive cells that impede the function of other fully activated effector immune cells. In spite of significant progress that have been achieved in increasing our understanding in this field, it is unknown whether all tumor cells exert similar inhibitory effect on the immune system or only specific subset(s) of tumor cells possess this feature.

There is accumulating evidence that cancer is originated and sustained by a small population of cells called "Cancer Stem Cells (CSCs)". These cells share many characteristics of the normal stem cells including the selfrenewing ability. Thus, it is possible that they also have the immune privilege properties of normal stem cells. At least this has been shown to be the case for two types of cancers: melanoma and glioma.

In this report we will review the role of CSCs in the creation of immune suppressive microenvironment which finally leads to tumor escape from the immune system surveillance.

**Keywords:** Cancer stem cells; Glioma; Melanoma; Epithelial-tomesenchymal-transition; Immune response

## **Introduction and Background**

The incidence of cancer is increasing worldwide and in spite of the significant advances achieved in cancer treatment, the mortality resulting from this disease is high. Cancer is a complex disease where transformed cells acquire various biological features that are essential to the initiation and maintenance of the disease. These features include: enhanced proliferative signaling, evasion of growth suppressors, increased resistance to death, enabled replicative immortality, induced angiogenesis and activated invasion and metastasis, reprogrammed energy metabolism and evaded immune system [1].

In most cancer cases, it is believed that increased mortality happens due to residual cancer cells remaining after surgery and/or induction of chemotherapy [2]. This residual population leads to disease relapse and/or tumor metastasis to other organs [3]. Successful cure for cancer is largely dependent on effective immune system that can detect and combat these cells to clear them from the system in addition to other established treatments like surgery and chemotherapy. In many cancer cases there are several signs of immune system activation against cancer cells, nevertheless some tumors keep growing [4]. This immune tolerance to tumor cells is attributed to the upregulation of regulatory molecules and/or release of suppressive factors in the tumor microenvironment [5]. However, the tumor tissue component that contributes directly or indirectly to the upregulation of regulatory molecules or the formation of the immune suppressive environment is not well-identified.

Normal tissues from different organs are maintained by "adult stem cells", which are cells with unique ability of continuous self-renewal and differentiation to specialized cell types [6]. Although they represent a small fraction of their respective tissue, stem cells are responsible for maintaining our cells homeostasis by replacing dead, injured and malfunctioning cells. Their proliferation is partially regulated by their supportive microenvironment cells usually termed as "niche" [7].

In cancer, a small subset of the tumor acquires some of the stem cell features and thus named as "cancer stem cells" (CSCs) [8]. Although still not definitive, there is mounting evidence that a hierarchy exist, where CSCs differentiate into cancer non-stem cells and form the bulk of the tumor [9]. Evidence show that in experimental settings, CSCs are solely responsible for the generation of tumors when implanted in immunocompromised mice, while their differentiated counterpart cells are not [10]. Importantly, recent supporting evidence confirms such a hierarchy even in unperturbed tumor model using genetic tracking systems [11-13]. While CSCs only represent a small fraction of malignant cells, they have been shown to be resistant to radiotherapy [14] and chemotherapy [15] leading to relapse of cancer and metastasis [3], which is believed to be the main cause of increased cancer mortality. In this review we will focus on one of the hallmarks of cancer i.e. immune escape of cancer cells.

## **Immunogenicity of Stem Cells**

The immune system is designed to recognize cells expressing non-self antigens and clear them from the system. This process is tightly regulated and dependent on the activation of antigen-specific T cells by professional antigen presenting cells such as dendritic cells, macrophages or B cells, with dendritic cells being the most potent and widely believed to be the only one that can prime naïve T cells [16]. Activation of T cells is a multistep process that is triggered

\*Corresponding author: Hazem Ghebeh, Stem Cell & Tissue Re-engineering Program, King Faisal Specialist Hospital and Research Centre, Saudi Arabia, E-mail: hghebeh@kfshrc.edu.sa

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when their T cell receptors recognize cognate peptide-MHC class II complex on the surface of professional antigen presenting cells [17]. While this step provides critical signal for the initiation of the immune response, a second signal is required to ensure productive activation of T cells that leads to the clearance of the antigen-baring cells whether pathogen-infected or cancer cells. The second signal is provided by co-stimulatory molecules such as CD80, CD86, CD40 or adhesion molecules such as LFA-1 and ICAM-1 [18-21]. In contrast, there are negative co-stimulatory molecules like B7-H1 (also called PD-L1 and CD274) that suppress the immune response, thereby modulate the immune response [18]. In addition, it has been well documented that the presence of some soluble factors or certain cell types during the antigen presentation step influence the immune response either by generating the wrong type of immune response or by suppressing the immune response [5]. For example, presence of TGF- $\beta$ 1 during antigen presentation is known to induce regulatory T cells (a subset of T-cell population characterized phenotypically by being CD4+CD25+FOXP3+ and ability to inhibit effector T-cells function) [19]. Altogether, above show that deregulation of the tightly controlled immune response may result in immune escape of cancer cells.

# Immunogenicity of Embryonic Stem Cells

Recent studies showed that stem cells exhibit cytotoxic and phagocytic activities [20,21] and have a machinery for antigen presentation contrary to the previous concept that they are immunologically null [22]. This notion is further supported by presence of immune reactions to stem cells that are implanted for the sake of cell replacement in degenerative disease animal models. Nevertheless, stem cells from different organs and hierarchy still show many signs of immune-privilege when compared with differentiated cells. For example, embryonic stem cells have many signs of immune privilege [23] and are less susceptible to rejection than adult cells [24]. Furthermore, their immunogenicity is tremendously increased after differentiation [25,26]. Recently, embryonic cells were shown to be immunogenic, but their inherent immune privilege property promote the induction of tolerance by reducing the number of professional antigen presenting cells and increased expression of soluble factors that favor the generation of regulatory T cells [27]. In addition, cord blood stem cells have been shown to be immune privileged through the expression of B7-H1 (a negative co-stimulatory molecule that inhibit T-cell activation) and it is ability to induce regulatory T-cells [28]. Interestingly, reprogramming adult cells by merely introduction of four transcriptional factors to generate pluripotent stem cells (iPSC) did not have such immune privilege [29], suggesting the presence of other genetic differences between embryonic stem cells and iPSCs.

# Immunogenicity of Mesenchymal Stem Cells

Mesenchymal stem cells (MSCs) are a relatively rare population of cells in the bone marrow that are able to differentiate into bone, fat and cartilage. Although they are not yet established as true stem cells, i.e. if they are able to maintain a whole tissue *in vivo* from a single cell, they are clearly multi-potent both *in vitro* and *in vivo* [30]. The immunomodulatory role of MSCs *in vitro* is well-established which is reviewed by Abdi et al. [4]. MSCs inhibit T-cell proliferation [31], abrogate lysis by CD8+ cytotoxic T-cells [32] and increase the proportion of FOXP3+ T-reg [33]. The mechanism involved in MSC mediated immunomodulation is partially explained by their expression of the negative co-stimulatory molecule B7-H1 [34], and their ability to produce hepatic growth factor (HGF), IL-10, and/or TGF- $\beta$ 1. These immune-modulatory properties of stem cells made them an attractive therapeutic potential and explain their wide use in many clinical trials to treat variety of disorders like: severe graft-versus-host disease, tissue repair and treatment of some autoimmune disorders [30].

Unfortunately, in cancer tissues, MSCs support the growth of tumors and suppress the immune system. For example MSCs produce CXCL7 which in turn induce the synthesis of IL8, a strong inducer of CSC self-renewal capability [35]. In addition, IL-1 $\alpha$  which is present in the tumor environment [36] makes MSC promote the growth of cancer cells [37]. On the other hand, MSCs, mainly through their ability to recruit T-reg, can suppress the migration and proliferation of peripheral blood mononuclear cells (PBMC) and inhibit NK and cytotoxic T- cell (CTL) functions [38].

# The Immune-Suppressive Effect of Cancer Stem Cells (CSCs)

CSCs possess similar features to normal stem cells in their ability of inducing immune modulation. Unfortunately, possession of these features by CSCs contributes to their escape from the immune system recognition and thus failure of the treatment and tumor relapse. Therefore, there is growing interest in understanding the mechanisms that regulate CSC immune modulatory properties in order to develop more effective therapy that can eradicate these cells.

There are many signs that tumors in general show signs of immune tolerance. This is manifested by their ability to attract CD4+CD25+ FOXP3+ regulatory T-cells [39], their expression of B7-H1 [40], their lack of co-stimulatory molecules like CD80 and CD86 (positive costimulatory molecules that are required for optimal T-cell activation) and their occasional lack of MHC class I molecules [41]. In our previous work we have shown that immune inhibitory molecules like B7-H1 is expressed on tumor cells, B7-H1 is expressed on tumor infiltrating lymphocytes, and FOXP3+ regulatory T-cells are abundant in the tumor microenvironment in a group of breast cancer patients. The expression of these molecules correlated with tumors that were estrogen receptor negative, high histological grade and large tumor size [42,43].

In addition, we found a significant correlation between the expression the negative co-stimulatory molecule (B7-H1) and the actin-bundling protein (fascin) [44]. The latter is important for normal mature dendritic cells function particularly in regulating their morphology, binding with antigen-specific T cells and generation of a productive immune response [45-47]. Interestingly, induction of fascin expression in many types of tumor is always associated with bad prognosis and shorter survival [48]. Although there is no direct evidence yet for a role of fascin in the immune escape of breast cancer cells, our study demonstrated, in breast cancer model, a novel role of this protein in regulating metastasis associated genes. Strikingly, Chen et al. [49] used a xenograft mouse model to demonstrate that the selective targeting of fascin by a compound named "migrastatin" inhibits breast cancer metastasis into the lung.

CSCs are the only cells that are able to re-establish a tumor with its heterogeneity when injected in an immunocompromised host [10]. However, when the immune system is further compromised a large fraction of the tumor cells can form tumors and not just CSCs. This has been shown by Quintana et al where up to 28% of tumor cells could form a tumor when injected in severely compromised IL-2 receptor deficient NOD/SCID mice (NOD/SCID/IL-2R $\gamma^{-/-}$ ) and not with original NOD/SCID mice [50]. This suggests a degree of interaction between CSCs and host immune system as only CSCs can overcome a

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certain degree of leaky immune response present in NOD/SCID mice and not the bulk of the tumor. Altogether, these studies suggest that it is possible that CSCs among the cancer cells are immune privileged which protect the tumor from the immune system recognition at least initially at the early stages of tumor development. At least this has been shown to be the case in two type of tumors i.e. glioma and melanoma [51].

# CSCs in Melanoma

Melanoma is one of the main causes of death related to skin cancer and it is particularly resistant to therapy [52]. Melanoma CSCs have been identified as ATP-binding cassette sub-family B member 5 (ABCB5) positive [53]. Specifically, ABCB5+ melanoma CSCs had significantly lower expression of MHC class I compared with the bulk of melanoma cells. In addition, the negative co-stimulatory receptor B7-H1 was preferentially expressed by ABCB5+ CSCs compared with the bulk (ABCB5<sup>neg</sup>) of melanoma cells. These observations suggest a lower ability of CSCs to induce an immune response compared with the bulk of the tumor [54]. Indeed, ABCB5+ melanoma CSCs blocked mitogen-stimulated PBMC proliferation by 93% and this inhibition was significantly greater than that exerted by ABCB5<sup>neg</sup> bulk population. These findings provided strong evidence for the immune suppression property of melanoma CSCs and make it an attractive target for therapeutic intervention.

# **CSCs in Glioma**

Glioma is considered one of the most aggressive malignancies of

the brain and central nervous system [55,56]. Like many other type of cancer, the glioma microenvironment become immune suppressive where primed CD8+ cytotoxic T-cells become inhibited or induced to become apoptotic and thus cannot execute their function [57,58]. In addition, there is increased recruitment of other immune suppressive cells like FOXP3+ regulatory T-cells [59]. Importantly, recent work has shown that this suppressive effect is specially exerted by glioma CSCs. This small subset of glioma cells, characterized by being CD133+ glioma cells (i.e., glioma CSCs), specially was able to inhibit T-cell proliferation and induce T-cell apoptosis via cell-to-cell mediated fashion and B7-H1 appears to play a central role in this process [60]. Indeed, inhibition of T-cell activation by the presence of CSCs to the co-culture was partially reversed by the addition of B7-H1 blocking antibody [60]. This is not to mention that glioma CSCs produced cytokines like TGF-1, CCL-2 and prostaglandin E2, which either prompt the propagation of FOXP3+ regulatory T cells, skewed the immune response into Th2 (not effective against cancer) or employed a global immunosuppressive effect. Importantly, glioma CSCs were shown to specifically produce galactin-3 leading to T-cell apoptosis [60].

In addition to the direct immunosuppressive effect of glioma CSCs, they recruit regulatory/suppressive cells which in turn modulate the immune response. For example, glioma CSCs induce FOXP3 regulatory T-cells partially involving B7-H1 molecule [60]. Furthermore, glioma CSCs, and not the bulk of the tumor, induce the differentiation of immune suppressive/tumor supportive type of macrophages (M2) from monocytes which is believed to be mediated through secreted macrophage inhibitor cytokine 1 (MIC-1) [61]. Interestingly, many



of the suppressive effect of glioma CSC could be reversed specifically by signal transducers and Activators and Transcription 3 (STAT3) pathway [62]. Altogether, these factors contribute directly or indirectly to the immunosuppressive property of glioma CSCs and further validate the notion that CSCs are an important subset of cancer cells responsible for the tumor escape from immune recognition.

# The Role of Cancer Induced EMT and Tumor Immune Escape

Breast cancer is one of the most common type of tumor in women [63]. While recent years have witnessed significant advances in the treatment of breast cancer, breast cancer mortality remained high mainly due to residual cancer cells that are therapy resistant and are able to re-grow and metastasize [3]. Many scientists believe that this subset of cells is able to do so via a process called Epithelial to Mesenchymal Transition (EMT) whereby epithelial cells lose their cell-to-cell junctions and gain features of mesenchymal cells like higher migration, and invasion. This process is paralleled with a change in some of the cell surface markers like CD44, CD24, vimentin and E-cadherin. Mesenchymal cells have a CD44<sup>high</sup>/CD24<sup>low</sup>, vimentin+ and E-cadherinneg phenotype, while epithelial cells normally have CD24<sup>high</sup>, vimentin<sup>neg</sup> and E-Cadherin+ phenotype. During the EMT process epithelial cells acquire the CD44<sup>high</sup>/CD24<sup>low</sup> phenotype, upregulate vimentin and down-regulate E-Cadherin. Importantly, there is an established link between this process and the gain of stem cell functions in breast cancer [64]. This includes the ability to grow in anchorage independent conditions and to reestablish tumors in mice models even when a very small number of cells are transplanted. Interestingly, when breast cancer cells were induced to go through EMT process under the influence of the transcriptional factor Snail, an EMT inducing gene, they promoted the escape of breast cancer cells from T-cell mediated lysis by CD8+ cytotoxic T cells [65]. This further supports the role of CSCs in the immune escape of breast cancer cells. This effect is not limited to breast cancer but was also found to be relevant to melanoma. Melanoma cells induced to go though EMT under the influence of Snail generated CD4+FOXP3+ T-reg and impaired the maturation of dendritic cells both in vivo and in vitro [66]. Collectively, the above data support that EMT, a process that enrich for CSCs, exhibit immunomodulatory property.

#### Conclusion

Despite the controversies regarding the existence of CSCs and their exact phenotype, mounting evidence is accumulating to support the importance of this unique subset of tumor cells. There are several evidences that CSCs employ immunosuppressive effect, thereby evading the immune recognition. Different CSCs may employ different mechanisms to confer this immunosuppressive effect either directly by regulating the expression of molecules such as the negative immune regulator molecule like B7-H1 or indirectly by influencing the tumor microenvironment to dictate the type of immune cell generated by favoring the induction or recruitment of FoxP3+ T-reg (Figure 1). These findings attract therapeutic intervention that involves targeting these CSCs and their immunosuppressive effect.

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