Cancer Stem Cells and Inflammation

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ABSTRACT

Cancer stem cells are cancer cells that possess characteristics associated with normal stem cells, specifically the ability to give rise to all cell types found in a particular cancer sample. It is often considered to be associated with chemo-resistance and radio-resistance that lead to the failure of traditional therapy. Cancer stem cells are the fourth leading cause of cancer-related deaths in women in the world and the leading cause of gynecologic cancer deaths. The major limiting factor in the treatment of cancer is recurrence and chemoresistance. Individuals who succumb to advanced stage cancer inevitably become refractory to chemotherapy, resulting in disease progression and death. The source of recurrence and lack of response to chemotherapy is unknown. The focus of this review is to evaluate the question of recurrence and chemoresistance based on the concept of the cancer stem cells and inflammation.

INTRODUCTION

Epithelial cancer is the fourth leading cause of cancer-related deaths in women in the world and the leading cause of gynecologic cancer deaths. The major limiting factor in the treatment of cancer is recurrence and chemoresistance. Individuals who succumb to advanced stage cancer inevitably become refractory to chemotherapy, resulting in disease progression and death. The source of recurrence and lack of response to chemotherapy is unknown. The focus of this review is to evaluate the question of recurrence and chemoresistance based on the concept of the cancer stem cells and inflammation.

Cancer Stem Cells:

Cancer stem cells are cancer cells that possess characteristics associated with normal stem cells, specifically the ability to give rise to all cell types found in a particular cancer sample. It is often considered to be associated with chemo-resistance and radio-resistance that lead to the failure of traditional therapy [1]. There show to be several sources from which cancer stem cells may happen. They may happen from normal ASCs (adipose-derived stromal cells), from more restricted progenitor cells or even from differentiated cells [2]. Normal stem cells are more likely to be the targets of mutants and leading to the formation of CSCs for they already possess active self-renewal pathways. It is also possible for progenitors and other differentiated cells to give rise to CSCs, though they would have to acquire more genetic mutations, especially in self-renewal genes [3-5]. Cancer stem cells can represent approximately 0.1–10% of all tumor cells and their antigens are typically expressed at lower levels than the ‘established’ tumor-associated antigens. Unlike these, the discovery of CSC antigens was not based on their over-expression but due to their presence on populations of cells which had stem cell-like properties. However, it has been hypothesized that CSCs arising from normal stem cells are more aggressive than those from progenitor cells, though this remains to be proven [6].

CSC Heterogeneity:

CSCs recently reported in mainly human tumors which can be identified using cell surface markers, such as CD44 and CD133 with flow cytometry, and functional approaches, including SP analysis [7-10]. The tumor

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cell subset that can set off tumor development at cell numbers with low percentage is enriched in CSCs. These cell surface markers have proved useful for isolation of subsets enriched for CSC. A most important surface markers are CD133, CD44, CD24, EpCAM (epithelial cell adhesion molecule, also known as epithelial specific antigen, ESA) [11-15]. CD133 is a transmembrane domain glycoprotein expressed on CD34+ stem and progenitor cells, in fetal neural stem cells. CD133 was also found in epithelial cells and in somatic stem cells from neural tissues, prostate, and kidney interestingly, human CD133+ cells from granulocyte colony stimulating factor-mobilized peripheral blood were able to differentiate into endothelial cells, when cultured in pro-endothelial lineage condition. In brain tumors, CD133+ cells revealed properties of cancer stem cells, and in the intestine, this marker identified stem cells that were susceptible to neoplastic transformation [16]. CD44 has pleiotropic roles in cell signaling, migration and homing. CD44 is considered a predictive marker for local recurrence after radiotherapy in patients with larynx cancer. High levels of CD44, aldehyde dehydrogenase and phosphorylated Stat3 are found in high-grade HNSCC, and are indicative of poor prognosis. Also, a higher frequency of CD44+ cells was observed in HNSCC that recurred than in human tumors without recurrence. Collectively, these studies suggest a direct correlation between CD44 expression, cancer stem cells, and the aggressiveness of head and neck tumors [17-20]. CD24 has co-stimulatory role in B and T cells. ALDH has role in conversion of retinol to retinoic acid, which is essential for survival. Breast CSCs (BCSCs) are the first CSCs to be reported in solid tumors and are among the most intensely studied ALDH1 is the prototypic member of the ALDH family and is highly expressed in human hematopoietic progenitors or hematopoietic stem cells.

MATERIALS AND METHODS

**TLR Expression and Function in Cancer:**

TLR activation by PAMPs and DAMPs has a critical role in innate and adaptive immunity. In addition to their expression on immune cells, TLRs are also expressed on the epithelial cell lining, gastrointestinal tract, and female reproductive tract, alveolar and bronchial epithelial cells in the lung, normal keratinocytes in skin, as well as vascular smooth muscle and endothelial cells in the cardiovascular system. TLR expression on the epithelial cell lining of an organ provides the first line of defense against pathogens and neoplastic lesions and is also important in the regulation of epithelial proliferative and apoptotic response [21]. TLR 1, 2, 4, 5, 6, and 10 are cell surface proteins and TLR 1, 2, and 6 respond to various lipoproteins and glycolipids of bacterial origin. TLR10 is the only TLR without a known agonist but does share the greatest homology with TLRs 1 and 6 and has been shown to colocalize with TLR2 in phagosomes [10, 11]. TLR5 responds to bacterial flagella, whereas TL4 responds to bacterial lipopolysaccharide (LPS) as well as DAMPs including S100A, HMGB1, and HSP released from apoptotic cells. Saturated fatty acids but not unsaturated fatty acids also activate TLR4. In recent years, TLR expression in tumor tissue has been reported, which may provide an important mechanism in the recruitment of inappropriate immune enhancement and dysfunctional immunity leading to antitumor immune tolerance [19]. One of the major challenges in understanding the connection between inflammation and cancer is to identify the triggering events that lead to the inflammatory response, the source and target of the inflammatory signals, and how this can contribute to tumor progression.

**RESULTS AND DISCUSSION**

**Cancer Stem cells and TLRs:**

Toll-like receptors (TLRs) are a family of transmembrane proteins, which recognize and respond to conserved pathogen-associated molecular patterns (PAMPs) that are expressed by microorganisms. To date, ten human TLRs and their specific ligands have been identified. Although TLRs individually respond to limited ligands, collectively as a family, TLRs respond to a wide range of PAMPs associated with bacteria, viruses, fungi and parasites. TLR-2 (with -1 or -6), -4, -5 and -9 recognize mainly bacterial products, while TLR-3 and -8 detect viral components. In addition, some TLRs, such as TLR-2, -4 respond to endogenous “stress” proteins, such as heat shock protein (Hsp 60), hyaluronan and fibrinogen [22, 23]. It should be noted that most of these endogenous ligands are released as part of cellular debris following cell death [24]. Most TLRs signal through a common pathway since they possess a common intracellular domain known as the Toll/IL-1R homology region (TIR). Following TLR ligation, the TIR recruits the adapter protein MyD88, which then leads to downstream activation of the NfκB and MAP kinase signaling pathways, resulting in an inflammatory response, which is characterized by the production of cytokines and chemokines.26 TLRs are widely expressed by the cells of the immune system, and initiate an inflammatory process in response to microbial products or stress factors [27-29]. In addition, TLRs have been described in non-immune cells, such as mucosal epithelium and trophoblast cells [21-25]. Similar to immune cells, the ligation of TLRs in non-immune cells results in the expression and secretion of pro-inflammatory cytokines [26].
REFERENCES


