

Tumor suppressor maspin as a modulator of host immune response to cancer

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ABSTRACT

Despite the promising clinical outcome, the primary challenge of the curative cancer immunotherapy is to overcome the dichotomy of the immune response: tumor-evoked immunostimulatory versus tumor-induced immunosuppressive. The goal needs to be two-fold, to re-establish sustainable antitumor-cancer immunity and to eliminate immunosuppression. The successful elimination of cancer cells by immunosurveillance requires the antigenic presentation of the tumor cells or tumor-associated antigens and the expression of immunostimulatory cytokines and chemokines by cancer and immune cells. Tumors are heterogeneous and as such, some of the tumor cells are thought to have stem cell characteristics that enable them to suppress or desensitize the host immunity due to acquired epigenetic changes. A central mechanism underlying tumor epigenetic instability is the increased histone deacetylase (HDAC)-mediated repression of HDAC-target genes regulating homeostasis and differentiation. It was noted that pharmacological HDAC inhibitors are not effective in eliminating tumor cells partly because they may induce immunosuppression. We have shown that epithelial-specific tumor suppressor maspin, an ovalbumin-like non-inhibitory serine protease inhibitor, reprograms tumor cells toward better differentiated phenotypes by inhibiting HDAC1. Recently, we uncovered a novel function of maspin in directing host immunity towards tumor elimination. In this review, we discuss the maspin and maspin/HDAC1 interplay in tumor biology and immunology. We propose that maspin based therapies may eradicate cancer.

KEY WORDS: Anticancer immunity; immunosuppression; immunogenicity; cancer immunoediting; innate immunity; adaptive immunity; serine protease inhibitors; tumor suppressor; maspin; autoantigen; differentiation; epigenetic; cancer stem cells; cellular plasticity; tumor heterogeneity

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CANCER IMMUNOTHERAPY, A DOUBLE-EDGED SWORD

According to the American Cancer Society, cancer is rapidly becoming a global pandemic and a leading cause of death worldwide (<http://www.cancer.org/>). It is estimated that there will be 1,658,370 new cancer cases diagnosed and 589,430 cancer deaths in the US in 2015. Recently, cancer immunotherapy is deemed to be one of the most promising avenues in cancer treatment, at least in part, by activating the natural host immune defense mechanisms. Of note, an ideal curative cancer immunotherapy should be both efficient and sustainable. During the past two decades, we have learned that the immune system in cancer plays a dual role: it can inhibit

tumor growth by killing cancer cells, or it can have an immunosuppressive role thereby promoting tumor progression and metastasis [1]. In the co-evolution with a tumor, the host immunity is thought to undergo three phases: elimination, equilibrium, and escape [2]. During the elimination phase, the cancer immunoediting is directed towards antitumor immunity, and it mainly depends on the expression of tumor-associated antigens (TAAs) presented by major histocompatibility complex (MHC) class I molecules. Consequently, tumor cells are eliminated by adaptive immunity through the activation of cytotoxic CD8⁺ T-cells and NK-cells, and by innate immunity through the activation of antitumor macrophages (M1 subtype), antitumor neutrophils (N1 subtype), and granulocytes [3]. At the equilibrium phase, cancer cells may escape by repressing the host immunogenicity. For example, the accumulated genetic and epigenetic changes in tumor cells may result in reduction or loss of TAAs expression or MHC-I molecules thus inducing the tumor escape mechanism. Therefore, this phase may feature a net immune inactivation due to the

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counter effects of immunosurveillance and immunosuppression. During the escape phase, the tumor cells may become fully non-immunogenic, and finally survive the already weakened immunosurveillance.

The ever changing tumor cells are considered the dominant driving force for the progressive decrease of the host immune surveillance partly due to the production of various immune modifiers. Tumor cells and their immediate micro-environment may accumulate immunosuppressive cytokines and chemokines such as interleukin 10 (IL-10) and transforming growth factor beta (TGF- β). These immunosuppressive molecules can inhibit cytotoxic CD8⁺ T-cell proliferation and stimulate proliferation and activation of immunosuppressive regulatory T-cells or myeloid-derived suppressor cells (MDSCs) [4]. On the other hand, tumor cells are known to convert the antitumor innate immune cells to pro-inflammatory cells that further facilitate tumor survival and invasion [5]. For example, it has been shown that the pharmacological blockade of TGF- β (secreted by both cancer cells and immune cells) within the tumor microenvironment can induce neutrophil switching from N₂, pro-tumor phenotype, to N₁, antitumor phenotype [5]. The dichotomy between antitumor and pro-tumor immune reactions remains a major challenge in the development of cancer immunotherapies. The field needs to explore innovative approaches to develop sustainable immunotherapy through the combination of drugs that can block the plastic changes on the cancer side that may evoke immunosuppression.

NON-INHIBITORY SERINE PROTEASE INHIBITORS (SERPINS) IN IMMUNOMODULATION

A great deal of efforts has been made in the search for TAAs for cancer immunotherapy. Previously, the TAAs presented by MHC-I molecules were categorized into different classes based on various molecular criteria such as whether or not they are: overexpressed or exclusively expressed by the cancer cells, encoded by tumorigenic transforming viruses, commonly expressed in fetal tissues and in cancer cells, commonly expressed by cancer cells and adult reproductive tissues such as testis and placenta, cancer histotype and differentiation lineage specific, or idiotypic proteins [6]. In addition, TAAs may belong to a variety of protein families that are structurally and functionally distinct such as SERPINS [6].

SERPINS share a general frame of structure but have diverse functions that may be involved in normal biological and pathological processes such as blood coagulation, fibrinolysis, apoptosis, development, inflammation, and tumorigenesis [7]. A phylogenetic study of the SERPINS superfamily divided the eukaryotic SERPINS into 16 clades (termed A-P), 9 of which

are found in humans [8]. Based on their activity or interaction with a target molecule, SERPINS may be classified into inhibitory or non-inhibitory SERPINS [8]. Inhibitory SERPINS, also known as "suicide" protease inhibitors insert part of their own reactive center loop (RCL) following cleavage by the protease, a hallmark of all inhibitory SERPINS, into the center of β -sheet A to form an extra strand thereby irreversibly inhibiting the enzyme [7]. Examples of inhibitory SERPINS include α_1 -antitrypsin and anti-thrombin among others [7]. Non-inhibitory SERPINS may function as storage proteins such as ovalbumin which is commonly found in chicken egg-white, hormone transporters such as cortisol-binding and thyroxine-binding globulins, and molecular chaperones such as heat shock protein 47 (HSP47).

To date, it remains unclear what turns a molecule into a TAA since it can be found intracellularly, on the cell surface bound or as a secreted protein [9]. As mentioned above, some of the members of SERPINS superfamily were previously characterized as antigens in cancer and autoimmune disease and as regulators of immune homeostasis [10-13]. For example, squamous cell carcinoma antigen-I is an inhibitory SERPIN that actively inhibits cathepsins L and V [7]. It is typically expressed by normal epithelial cells and B-cells, but it was shown to function as a TAA in hepatocarcinoma and cervical cancer [10,14,15]. In addition, it also functions as an autoantigen in two autoimmune diseases: psoriasis, a chronic inflammatory skin disease [11] and lupus erythematosus, a systemic autoimmune disease [16]. Interestingly, ovalbumin, a major storage glycoprotein in chicken's egg, was demonstrated to be a driving antigen of egg allergies, the second most common food allergy in infants and young children [12,13]. Another SERPIN important for maintenance of immune homeostasis is centerin [17]. Centerin was shown to regulate the survival of naïve B-cells and the development of germinal centers of secondary lymphoid organs which are sites of B-cells differentiation. Finally, we have recently shown that re-expression of tumor suppressor maspin, an ovalbumin-like non-inhibitory SERPIN, in prostate tumor cells stimulates an antitumor immune response, leading to tumor elimination *in vivo* [18]. Moreover, maspin is an epithelial specific 42 kDa that acts as an endogenous inhibitor of histone deacetylase (HDAC1) [19,20].

THE BIOLOGICAL FUNCTIONS OF MASPIN IN TUMOR CELLS

The most reproducible biological effect of maspin in tumor progression is the inhibition of tumor invasion and metastasis [21]. For example, in a severe combined immunodeficiency (SCID-Hu) mouse model for prostate cancer bone metastasis, maspin expression in prostate cancer induced

tumor cell redifferentiation and blocked tumor-induced bone remodeling [22]. The metastasis-promoting effects of IKK α in the transgenic adenocarcinoma of mouse prostate (TRAMP) model for prostate cancer were, at least in part, a result of maspin repression [23].

The tumor suppressive effects of maspin are attributed to its effect on gene expression reprogramming in favor of supporting better differentiated epithelial phenotype and increased sensitivity to drug-induced apoptosis [24,25]. Although maspin is an epithelial-specific protein, its impact on tumor cell biology may not be restricted to epithelial cells. We have shown that the effects of maspin are sensitive to changes of the tumor microenvironment and may have an important impact on the integrity of the tumor stroma [15,22]. For example, maspin expression in tumor cells increases fibrosis, blocks tumor angiogenesis, blocks extracellular matrix degradation, and bone remodeling [22,26]. In a recent study, we also showed that maspin inhibits cancer stem-like potential and stratifies drug sensitivity of prostate cancer cells [26,27]. Since cancer stem-like cells may be more resistant to chemotherapy and immunotherapy [28], it is intriguing to speculate that maspin or maspin-mimicking drugs in combination with conventional cancer treatments may re-sensitize cancer cells to chemotherapy due to inhibition of the cancer stem-like phenotype. In clinical settings, maspin down-regulation is correlated with the progression, mostly at the step of tumor invasion, of at least 15 different types of cancer [29]. Consistent with the molecular interaction between maspin and nuclear HDAC1, in benign prostate epithelium, maspin is localized predominantly in the nuclei of basal cells, whereas in high grade prostatic intraepithelial hyperplasia (high-grade prostatic intraepithelial neoplasia (HGPIN)), maspin expression is significantly increased and is translocated to the cytoplasm. Maspin is progressively down regulated at the transition to invasive and high-grade prostate cancer [30]. In lung adenocarcinoma, nuclear maspin was shown to be a typical feature of the lepidic growth pattern, whereas increased and combined nuclear and cytoplasmic maspin followed by the loss of maspin characterized the invasive phenotype [31]. This clinical observation raises the possibility that apparent loss of maspin expression in invasive carcinoma may be a consequence of the elimination of maspin-expressing tumor cells, by host immunity.

A ROLE OF MASPIN IN MODULATION OF THE HOST IMMUNITY

Indeed, there are several recent reports that support the idea that maspin may function as a modulator of the immune system in the tumor microenvironment. Specifically,

maspin expression correlates with preeclampsia [32-34], which is characterized as a pregnancy-induced autoimmune condition [35]. Maspin may function as an autoantigen in HLA-Cw6-associated T-cell-mediated psoriasis [36]. Maspin expression also correlates with the activation and proliferation of a fraction of CD8⁺ T-cells in a certain subset of psoriatic patients. We were the first to investigate the role of maspin in tumor-evoked host-immune response [18].

Using athymic nude mice, which are B-cell competent and support the growth of xenogeneic human prostate cancer cells, we demonstrated that maspin expressing prostate cancer cells were partially eliminated by antitumor innate and humoral immunity [18]. Our histological analysis of tumors revealed reorganization of the tumor mass in maspin expressing tumors resembling epithelial-like nodules associated with tumor necrotic foci due to increased neutrophil chemotaxis, infiltration, and cytotoxicity. Splenocyte analysis of tumor bearing mice revealed a significantly larger proportion of anti-tumor "N1" state (7/4 + CD11b + Ly6G^{high}) neutrophils in mice bearing maspin expressing tumors as compared to the controls. Previously, we showed that maspin regulates the transcription of multiple genes encoding for cytokines and chemokines such as IL-8, IL-24, chemokine (C-X-C motif) ligand 10, tumor necrosis factor (ligand) superfamily (TNFSF) 10, and TGF- β that may be important in neutrophil activation and migration so the fact that we see neutrophil-mediated cytotoxicity of maspin expressing tumors should not be surprising [27]. In addition, we also demonstrated that the activation of neutrophils by maspin may be B-cell dependent since we showed that mice bearing maspin expressing tumors had elevated expression of tumor-cell reactive and maspin-specific immunoglobulin G (IgG). Although B-cell response is thought to be primarily dependent on CD4⁺ T-cell interaction, recent studies showed that neutrophils can promote the differentiation and activation of B-cells independently of CD4⁺ T-cells [37,38]. This was the first evidence demonstrating the function of maspin as an epithelial-specific antigen in cancer disease.

Experimental evidence suggests that maspin can also be found cell-surface associated or as a secreted protein [39]. Thus, it is possible that maspin may directly serve as a TAA. On the other hand, as an epithelial-specific HDAC1 inhibitor [19,40], the biological effects of maspin on immune cells may be indirect. It is important to note that a number of pharmacological HDAC inhibitors (HDACi) have been approved by the FDA for the treatment of solid and hematopoietic tumors [41]. Taking into consideration that HDACs are ubiquitously expressed by all cell types, including immune cells, systemic administration of HDACi would not only exert cytotoxicity to tumor cells but also affect all the cells that express HDAC1. Indeed, HDACi were shown to modulate

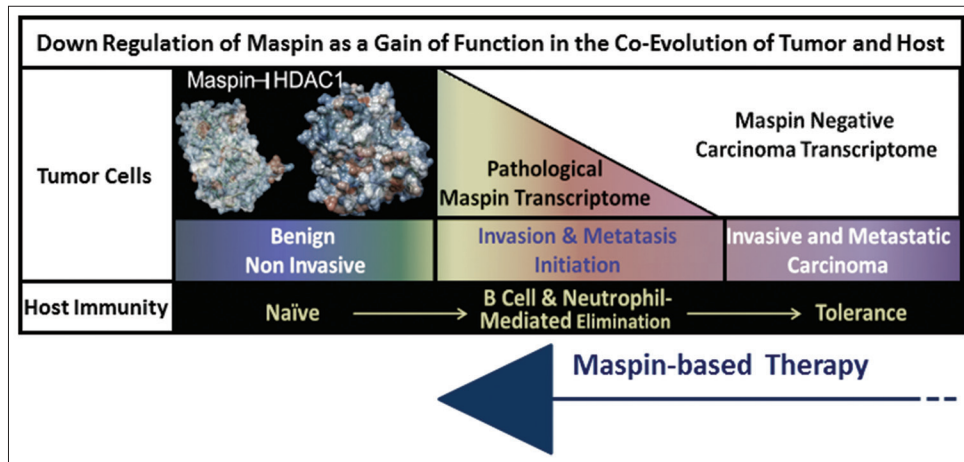


FIGURE 1. An overarching hypothetical model for the regulation of epithelial transcriptome in tumor progression and the co-evolving host immune response. This model emphasizes the inhibition of histone deacetylase 1 as the underlying mechanisms for the biological functions of maspin and suggests the therapeutic potential of novel maspin-based drugs in eliminating invasive and metastatic cancer.

the immune response of innate and adaptive immunity [42]. Specifically, they may either increase or decrease TAAs expression and presentation by tumor cells and may cause the activation of either antitumor cytotoxic CD8⁺ cells or pro-tumor regulatory T-cells [42-47]. Interestingly, depending on the molecular context, tumor type and stage of the disease and timing of drug administration, the net immunological impact of HDACi may be either stimulatory or suppressive. This diverse immunological consequence of HDACi that is not HDAC isoform- or cell type-specific underscores the biological necessity to have specific HDAC isoforms regulated by cell type-specific inhibitors such as maspin.

CONCLUSION AND FUTURE DIRECTIONS

As summarized in Figure 1, our view of the role of maspin in the regulation of epithelial homeostasis and tumor biology is extended into its broader biological consequence through immunomodulation. Specifically, maspin may increase the tumor cell antigenicity by depleting cancer cells of the stemness so they cannot camouflage in mesenchymal phenotypes, by regulating the HDAC₁-dependent cytokine expression profile to reduce immune suppression, and by acting directly as an epithelial-specific TAA. Therefore, as compared to the pharmacological HDACi or immunotherapy, maspin or maspin-mimicking drugs may have an advantage of dually targeting aggressive tumor phenotype and the insufficiency of host immunity. This maspin-based therapy may constitute a significant advancement in immunocombination therapy, even for advanced diseases, since it can reverse the tumor cells to less aggressive and better differentiated phenotype while shifting the host immunity from tolerance or equilibrium to elimination mode.

DECLARATION OF INTERESTS

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