Immune privileges as a result of mutual regulation of the immune and stem systems.

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Abstract

Accumulating evidence shows that both normal and cancer stem cells exhibit immune privileges. This review focuses on stem cell immune privileges as a function of non-pathological stem cells related to autoimmunity control and regeneration. Based on the diversity in the regulation of stem cells, their microenvironment and the immune system, I propose the use of the term "stem system".

Key words: Autoimmunity, regeneration, stem cell, cancer stem cell, stem system, immune privileges, nestin

Introduction

The development of surgery and, in particular, transplantation techniques has led to the need to learn from animal models. This led naturally to the discovery of allogeneic graft rejection reactions and the discovery of immune privilege. The first mentions of immunoprivilege date back to the 19th century [1,2], when an ophthalmologist observed that a mouse skin graft planted in the anterior chamber of a dog's eye showed a longer survival time. In his work, Shirai showed engraftment of cancer cells grafted from a third-party donor into the brain, as opposed to rejection when grafted into other tissues [3]. Another work [4] showed that grafting a fragment of autologous spleen into the brain together with tumor cells leads to the death of the latter. It was also shown that prior immunization of the recipient leads to rejection of the skin graft in the mouse brain [5]. Work on the retina showed engraftment of GFP-expressing transgenic cells in a wild-type pig recipient without the use of immunosuppressants [6]. Initially, the main hypothesis was the existence of a region isolated from the cells of the immune system. However, it is also widely known that disruption of one eye can lead to an immune response and an attack on the contralateral eye [7]. The demonstrated migration of peripheral immune cells across the integral blood-brain barrier and the active regulation of macrophages and lymphocytes by neurons and glia [8] caused reconsideration of the view of immunoprivilegedness as a property of an organ region isolated from the immune system. One theory about mechanisms of placental and fetal immunoprivilegedness is associated with a layer of regulatory T cells expressing HO-1, LIF, TGF-β and IL-10 factors [9]. The immunogenicity of autologous sperm shown in the pig [10] also means that the testes are immunoprivileged. The mechanisms of immunoprivileged testes include both cellular barriers built by Sertoli cells [11] and mechanisms of cytokine regulation suppressing the immune response [12,13]. Melanocytes are able to migrate to hair follicles, where they are not destroyed by the immune system in heterotypic transplantation [14]. This allows to refer hair follicles to immunoprivileged regions of the body [14,15]. Mechanisms of immune privilege are also found in articular cartilage [16,17]. Of particular interest are cases of tumors using immune privilege mechanisms [18,19].

Immune privileges of stem cells

Earlier studies demonstrate the escape of stem cells from the cytotoxic action of immune cells for hematopoietic stem cells [20], embryonic stem cells [21], and further for mesenchymal [22] and neural stem cells [23]. Works show that decreased expression of the major histocompatibility complex (MHC) molecules removes surveillance from cytotoxic CD8+ lymphocytes and that natural killer (NK) cells do not attack stem cells regardless of MHC expression.

Recent work [24] demonstrates immune privileging as an intrinsic property of the stem cells considered in the article. The authors have done thorough work and have shown that it is possible to identify subpopulations of stem cells not subject to immune surveillance in hair follicles and muscle, but not in the gut, ovary or mammary gland. The quiescent state has been highlighted as a defining property of

subpopulations of stem cells escaping immune surveillance. The expression of major histocompatibility complex class I (MHC-1) and β2-microglobulin (B2m) was also reduced in these cells. A significant decrease in the expression of the receptors and transcription factors Irf3, Irf5, Stat1 and Stat3 responding to inflammation was also shown. The authors also showed that this subpopulation of stem cells does not activate effector T cells and is not affected by the immune system, but these properties are lost under stimuli that activate resting stem cell proliferation. The absence or significant decrease of MHC-1 on the cell surface should lead to NK activation and destruction of such cells by them, which was not observed in the described work. This implies the existence of other mechanisms to protect resting stem cells from immunity. Authors used CD8+ T cells, with a T-cell receptor affinity to GFP peptides within the MHC-1 complex, destroying GFP-producing cells in vivo.

Based on the results [24], of particular interest are long-repopulating hematopoietic stem cells (HSCs), which rarely divide and mostly remain quiescent [25], as well as mesenchymal stem cells (MSCs), since there is reason to believe that they are also prone to being quiescent in vivo [26]. The immunogenicity of the total mass of allogeneic bone marrow cells is beyond doubt [27,28], however, this does not exclude the possibility of the presence of minor cell populations with immunoprivileged cells. For example, work on mice has shown that CD150high regulatory T cells (T-reg) protect HSCs from oxidative stress and keep them dormant [29]. At the same time, the authors showed immune privileges of quiescent HSCs, but did not link the quiescent state and immune privilege as cause and effect.

The scientific position regarding the immune privileges of mesenchymal cells (MC) is ambiguous. Despite the background and demonstration of significant immunomodulatory potential [22], MC and MSC have been classified as cells without immune privileges [28,30-33]. However, work demonstrating immune privileges of resting stem cells [24,29], including cancer cells [34,35], leads to the association of mesenchymal cell phenotype with immune privileges [36]. In our recent work, we showed the immune privileges of MSCs in a model of ectopic hematopoiesis foci in mice [37]. Based on our results and literature data, we pointed out the relationship between nestin expression and the population of immunoprivileged cells. Such nestin-expressing stem cells are found in all parts of the adult organism, organs of various embryonic origin: as in the immunoprivileged cells we studied, particularly MSC, and other immunoprivileged stem cells, such as muscle stem cells and hair follicle stem cells [37], as well as stem cells from other immunoprivileged territories: testis [38], cartilage [39], brain [40], and retina [41]. It remains an open question whether nestin is a direct regulator in the processes of immune privilege formation or is only a passive marker. The question of nestin's involvement in immune privilege mechanisms has not been directly addressed in this work, nor has the question of immune privilege mechanisms in general.

Nestin is a type VI intermediate filament [42]. Nestin is known as a stem cell marker [42]. Increased expression of nestin is highlighted as a negative prognostic factor for a number of cancers of epithelial, mesenchymal and neural origin:

colorectal cancer, hepatocellular carcinoma, various central nervous system cancers, non-small cell lung cancer, breast cancer, melanoma and multiple myeloma [43]. Moreover, nestin is associated with immature tumor phenotype and cancer stem cells (CSCs) [44]. Hyperexpression of nestin is associated with more aggressive course and metastasis of tumors, their refractoriness to therapy [45].

Additional arguments about the commonality of stem cells of different tissues come from the works devoted to stem cells [46]. VSEL - very small embryo-like stem cells - are considered in the review [46]. Participation in reparative processes has been shown for such cells: their number increase and release into the peripheral blood under the action of tissue damage factors. Muse cells demonstrate the ability to cross-differentiate between the germ leaflet directions [47,48]. Thus, for a small subpopulation of MSCs, which can be found in the connective tissues of almost all organs, the authors demonstrated the ability of cells to differentiate in all three directions of the germ sheets. These cells are self-maintaining, move to areas of damage, express nestin and are a subpopulation of MSCs for which we have demonstrated immune privileges [37,47]. Together with the works showing that resting adult stem cells do not directly participate in tissue formation during embryogenesis [46,49-52], we can generalize that it is possible to identify subpopulations of stem cells of different organs and tissues of the adult organism having many common functions and characteristics (Fig. 1). It is unlikely that many different and independent mechanisms have evolved for the same functions, but a rigorous test of this hypothesis is required.

Stem system

A stem cell and its environment represent a complex system of their mutual regulation. Practical separation of a stem cell from a niche is difficult due to the disruption of cellular regulation [24,53-56]. Cultivation of the isolated stem cell subpopulation requires special solutions. For example, the effectiveness of cultivation methods aimed at keeping muscle stem cells in a quiescent state to increase the subsequent therapeutic effect in mice has been demonstrated [57]. These methods involve local regulation of stem cells by a niche including a matrix and a special growth medium. Microvesicles secreted by MSCs are able to interact with targets in other parts of the body [58,59]. For muscle stem cells, their transition to the state of readiness as a response to damage in another part of the body is demonstrated. [51]. Terminologically it is appropriate to talk about the existence of the stem system responsible for the regulation of its cellular and other components. This system performs the function of supporting the cellular composition of the organs of the adult organism, reacts with reparative response in case of damage, carries out interregulation with the immune system (Fig. 1). The term "stem system" will more accurately reflect the structure of the object of study, which should have a favorable effect on the overall presentation. At the same time, the separation of the concepts of stem cell and stem cell niche is crucial in understanding their functioning. Schemes of experiments capable of distinguishing the contribution of

individual cells or their subpopulations can offer a fundamentally new perspective on the object of study [37].

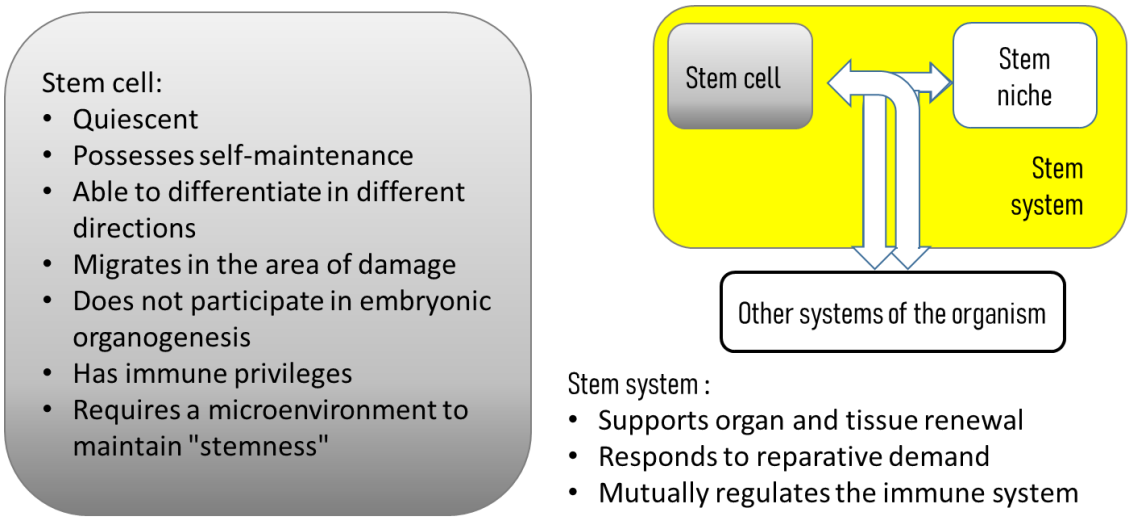

Figure 1 Schematic shows the idea of generalizing stem cells, their microenvironment and their regulatory mechanisms into a stem system.

Generalization of the characteristics of the body's stem cells and recognition of immune privileges as the main property of stem cell subpopulations gives a new perspective on the processes of carcinogenesis. CSCs are known to be associated with refractoriness to therapy, metastasis, relapses [60,61]. The literature demonstrates a systemic similarity between CSCs and normal stem cells expressed in the deep resting state, the ability to migrate and differentiate, resistance to hypoxia, self-maintenance, and nestin expression [37,42,44,46,48,60]. A number of studies have shown an inhibitory effect of the immune system on oncogenesis processes [62,63]. The presence of immune privileges in CSCs as stem cells provides significant advantages to pathological cells, which is demonstrated in experiments [34,64]. Thus, cancer cells can obtain a whole set of advantages characteristic of stem cells by shifting to the stem state instead of independent sequential accumulation (Fig. 2). At the same time, immunoprivileged territories can be used by infectious pathogens as a shelter from the action of the immune system [65]. Infection of stem cells and their niches leads to the impairment of the stem system functions and is expressed by clinical pathologies in the form of fibroses, hematopoiesis disorders, bone and cartilage disorders, damage of the barrier functions in the brain vessels [65].

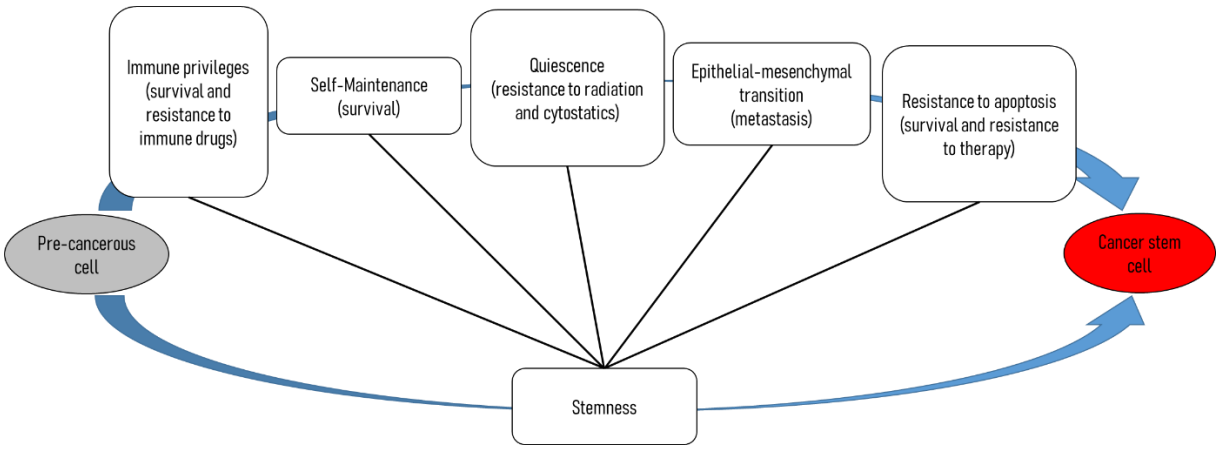

Figure 2 Figure shows the idea that in a number of cancer cases it is possible to obtain the set of traits necessary for cancer stem cell survival through the stem state rather than through independent events.

The presence of such a potentially dangerous mechanism as stem cell immune privileges must be evolutionarily counterbalanced by equally significant reasons, lest it be rejected in the process of evolution. Control of autoimmunity is an appropriate significant reason. In addition to the mechanisms of central control of autoimmunity, peripheral control mechanisms are present in the body [66,67]. The main peripheral control performers are considered to be T-reg, but the involvement of other immunity control mechanisms is also noted. Immune privileges of stem cells may be part of such mechanisms [68] (Figure 3). This assumption is supported by the fact that during the inflammatory process, MSCs do not simply evade the action of immune cells, but are also activated and secrete chemokines that attract immune cells [69,70]. The involvement of stem cells in the process of peripheral control of immunity may be due to the high value of such cells and the need to protect them. Also, peripheral control may be necessary in addition to central control, especially for complex, long-lived organisms that can accumulate mutational differences in the genome of peripheral tissues and the central immune system during their lifetime.

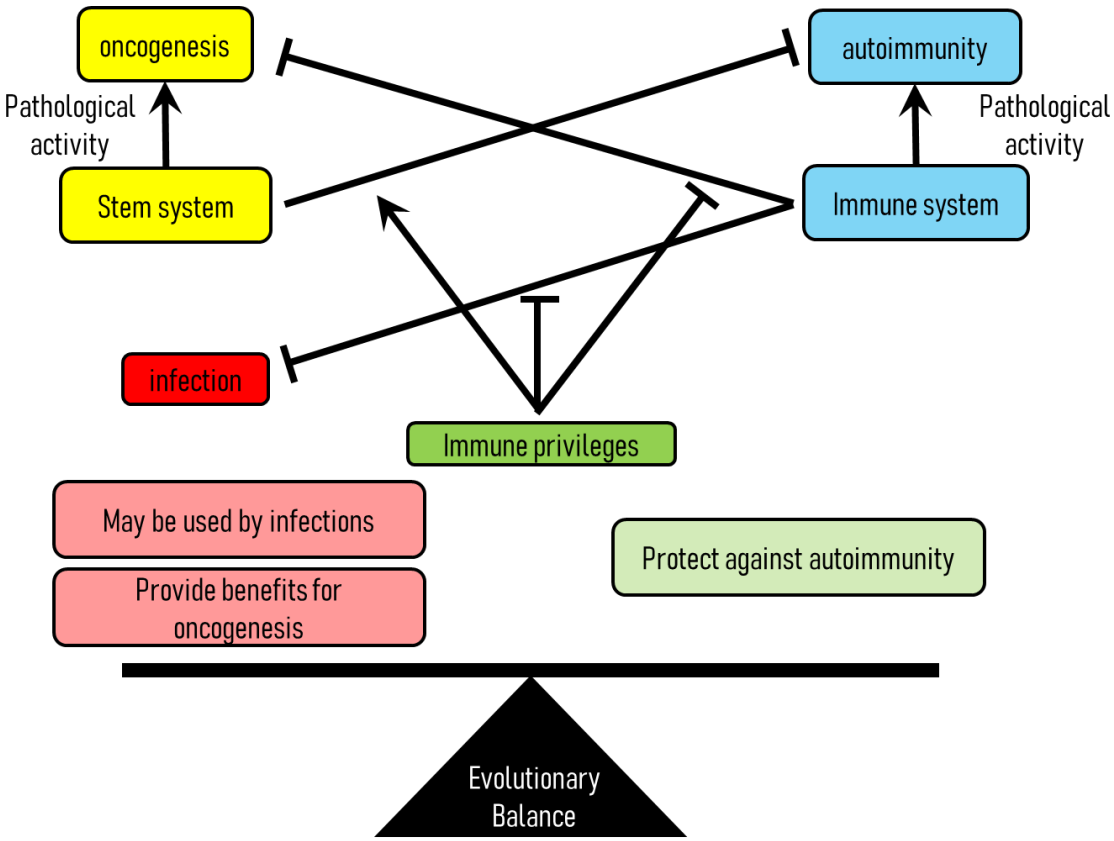

Figure 3 The diagram shows the possible role of immune privileges in the regulation of the stem and immune systems as a result of evolutionary balance.

In addition to autoimmune control, interaction between the stem system and the immune system is necessary at the site of injury. Properly orchestrated activation of repair and inflammatory programs is an important biological regulation [58,71,72]. The interaction between these functions appears to be even more important for evolutionary equilibrium, and it can use the same mechanisms as autoimmunity control (Figure 4).

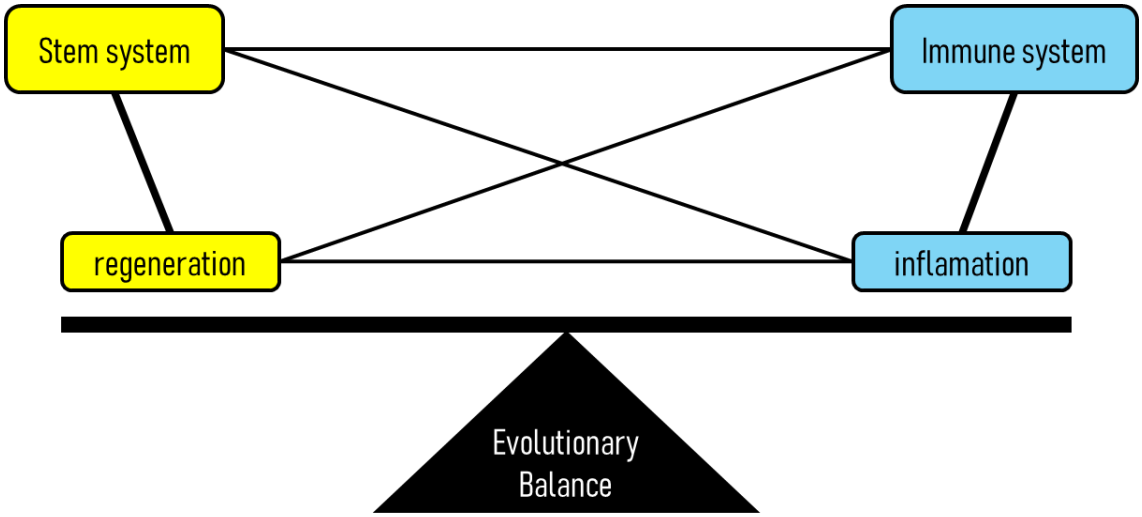

Figure 4 Schematic depicts the balance between regeneration and inflammation as part of the evolutionary balance between stem and immune system mechanisms.

The role of the immune system in the regulation of stem cells and their niches is described in the literature as mediated by T-reg cells and macrophages. The existence of tissue T-reg with the expression profile and transcriptome similar to that of stem cells has been demonstrated for T-reg [72]. The participation of T-reg in the processes of tissue repair, maintenance of the dormant state of stem cells and their differentiation has been shown [29,73,74]. JAG1 signal expression has been shown for T-reg residents of hair follicle stem niches, which means participation in Notch signal transmission, which plays an important role in stem cell regulation [75,76]. For macrophages, their role in the processes of repair of various tissues has been shown, and their dysfunction leads to dysregulation of stem cell differentiation and fibrosis [71]. Macrophages also support MSCs in the fight against oxidative stress through utilization of depolarized mitochondria [77].

In turn, stem cells along with immunosuppressive effects are able to stimulate the inflammatory response. Thus, MSCs activated by inflammatory signals release chemokines that attract immune cells to the damage area, where stem cells can modulate their further activity [69,70]. The hormone procalcitonin produced by MSCs is one of the best and earliest markers of various groups of infectious diseases [65,78]. Procalcitonin levels are significantly elevated long before C-reactive protein levels increase, which is used in intensive care units. MSCs also express functional Toll-like receptors (TLRs) that activate migration, differentiation, cytokine and chemokine secretion in response to pathogen-associated ligands [79]. Such MSCs have been shown to lose their ability to inhibit T-lymphocytes due to disruption of the Notch signaling pathway through TLR3 and TLR4 activation [79].

Integrating a new mechanism into the system creates a potential point of failure. For every mechanism, there are reasons that outweigh the risks associated with it, otherwise it is rejected by natural selection. Such deep integration of the stem system and the immune system means that there is an evolutionary necessity and a complex fine-tuned regulation. As can be seen from the review, the fundamental importance of immune privileges of non-pathological stem cells and especially MSC can hardly be overestimated. As MSCs are distributed throughout the body and demonstrate a strong contribution to immune regulation [49,58,59,69,70]. The interaction between stem and immune systems plays an important role for various aspects of damage regeneration and autoimmunity control [15,29,48,59,71,74,77]. The immunoregulatory properties of MSC are used for supportive transplantation therapy, and the regenerative potential of MSC is used in regenerative medicine [48,58,69]. Also immune privileges may be involved in the development of cancer and infectious diseases [34,35,64,65]. Thus, the subject matter of this review touches on a wide range of medical issues, including those not addressed in this review.

Conclusions

The association of immune privileges with the basic property of resting stem cells offers a perspective on the regulation of autoimmunity, infectious diseases, regenerative medicine, transplantation and oncology. Thus, in some cases, stem cell transformation can provide cancer stem cells with a range of benefits, including

protection from immunity. This insight could prove important for the treatment of cancers in which cancer stem cells are present. Studying the interaction between stem cells and immune cells reveals the existence of a complex network of mutual regulation, the disturbance of which can lead to cancer, autoimmune pathologies, organ tissue dysfunction and accelerated aging. Based on the existence of a complex network of regulation of stem cells, I propose to use the term "stem system", which includes both the regulation of stem cells themselves and their microenvironment, and the mechanisms of their interaction with the immune system. The term "stem system" allows to reflect more accurately the structure of the object of study, which will favorably affect the overall presentation. The study of mechanisms of regulation of the stem and immune systems offers great opportunities for the study of the capable, the results of which will allow to better understand the biology and apply the findings in medicine.

Contributions

Literature analysis and writing of the article was performed by Dmitry Karpenko

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Conflict of interest

The author declares that there is no financial or other conflict of interest in the submitted work.

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