Opinion

Immune modulating stem cells represent a significant component of the immune system.

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Abstract

Stem cells represent a vital component of the body's natural repair mechanisms, providing support for tissues with differentiating cells and responding to regenerative requests in damaged areas. Mesenchymal stem cells are additionally known for their immunomodulatory properties. The immunomodulatory properties of these cells are used in clinical practice for the treatment of immune-associated dysregulations. Mesenchymal stem cells and their derivatives are applied in organ and hematopoietic stem cell transplantation procedures for the treatment of autoimmune disorders and other conditions. Recently immune privileges for them and few other stem cells were demonstrated. Existence of stem cells immune privileges was reasoned by cross action between processes of regeneration and inflammation and as a part of peripheral control of autoimmunity. A new fundamental feature of stem cells requires integration into the general understanding of evolution and regulation of the stem system. I suggest a functional model which links the attributes of stem cells, including quiescence, response to regeneration request, immune modulation, and the maintenance of homeostatic differences, as well as their low percentage in tissues. I suggest that immune modulating stem cells (IMSCs) should be recognized as a relevant part of the immune system.

Keywords:

Stem cells, immune modulating stem cells, immune system, evolution, infections

Stem cells are an important compartment supporting tissues with differentiating cells and responding to the demand for regeneration in damaged areas [1–4]. There are interesting evidences that subpopulations of stem cells migrate to developing organs and tissues during embryogenesis, but do not directly contribute to development [5–10]. Such stem cells persist to provide support as stem cells of the adult organism. There should be additional functions apart from just building organs and tissues to justify maintenance of separate stem cells. This could rethink a question why the such stem cells are needed in adult. Idea that more cells would have proliferative and differentiation potential of stem cells seems good for regeneration, but it should be balanced with risks of mutations and oncogenesis. A self-maintaining, highly proliferative cell would need fewer changes to become a cancer cell. The quiescence of stem cells with high proliferative potential could be justified in the same way to place them evolutionarily further away from cancer cells [11]. Slow dividing cells also have a lower mutation potential associated with the number of divisions [12]. Lower mutational potential is associated with resistance to oncogenesis, as well as with a lower number of neoantigens and consequently lower autoimmunity [13]. These reasons are important, but in the context of long-living strategies, could there be benefits from keeping stem cells quiescent in the short-term? The quiescence of stem cells, coupled with their metabolic processes, enables them to survive in severely damaged tissues, thereby facilitating regeneration [14,15]. Given their role in regeneration, an increase in the number of stem cells would be expected to enhance the regenerative potential. It has been reported that there is one quiescent stem cell for 10^4-10^5 surrounding cells in circulating blood and other tissues in adults [16–21]. It is reasonable to posit that there are reasons to maintain this stem cell number at a relatively low level. An interesting note that an increased number of stem cells suggests lower number of divisions for each, this way significantly reducing a chance of a random cooperation of oncogenic mutations in a single cell, thereby lowering cancer risk [11]. An additional potential explanation is that it is a matter of energy consumption efficiency. However, a tenfold change in the number of stem cells results in a mere 0.1% alteration in the total value. It would be reasonable to inquire whether there is an additional, more compelling rationale. Recently, the immune privileges of stem cells have been demonstrated [20,22–24]. It was previously suggested that the immune privileges of stem cells are associated with their quiescent state and relate to regeneration and inflammation regulation [22,25]. I propose a generalized model that functionally links the newly demonstrated immune privileges to other attributes of immune modulating stem cells (IMSCs).

The functional significance of IMSCs is of particular evolutionary importance with respect to the stem and immune systems [25]. The reports indicate that mesenchymal stem cells not only evade cytotoxic immune action [26], but also actively attract immune cells and can reprogram them depending on the molecular context [27–30]. Immune modulation of stem cells is employed in the context of solid organ transplantation and is utilized in the treatment of autoimmune pathology [27–30]. This gives ground to mark MSCs as baring functional of immune suppression. The activation of MSCs and the subsequent induction of a regenerative program results in the suppression of the inflammatory program [29,31]. The suppression of inflammation is achieved through a variety of mechanisms, including cell-to-cell contact and paracrine regulation, whereby secreted molecules and microvesicles regulate the surrounding environment [29,31,32]. Immunomodulatory capabilities are more pronounced in IMSCs than in other differentiated cells [33,34]. It is challenging to determine where the immune or other functions of IMSCs are lost during differentiation to their progeny, particularly in light of the potential for dedifferentiation [35,36]. The existing mutual integration of stem and immune systems highlights the evolutionary significance of this integration, as an additional mechanism may potentially act as a break point. This underscores the necessity for evolutionary coordination

with respect to the attributes of immune and stem cells involved in this integration. The construction of a comprehensive model is hindered by the vast number of elements and the incomplete knowledge about their connections. Therefore, I propose a functional model (Figure 1).

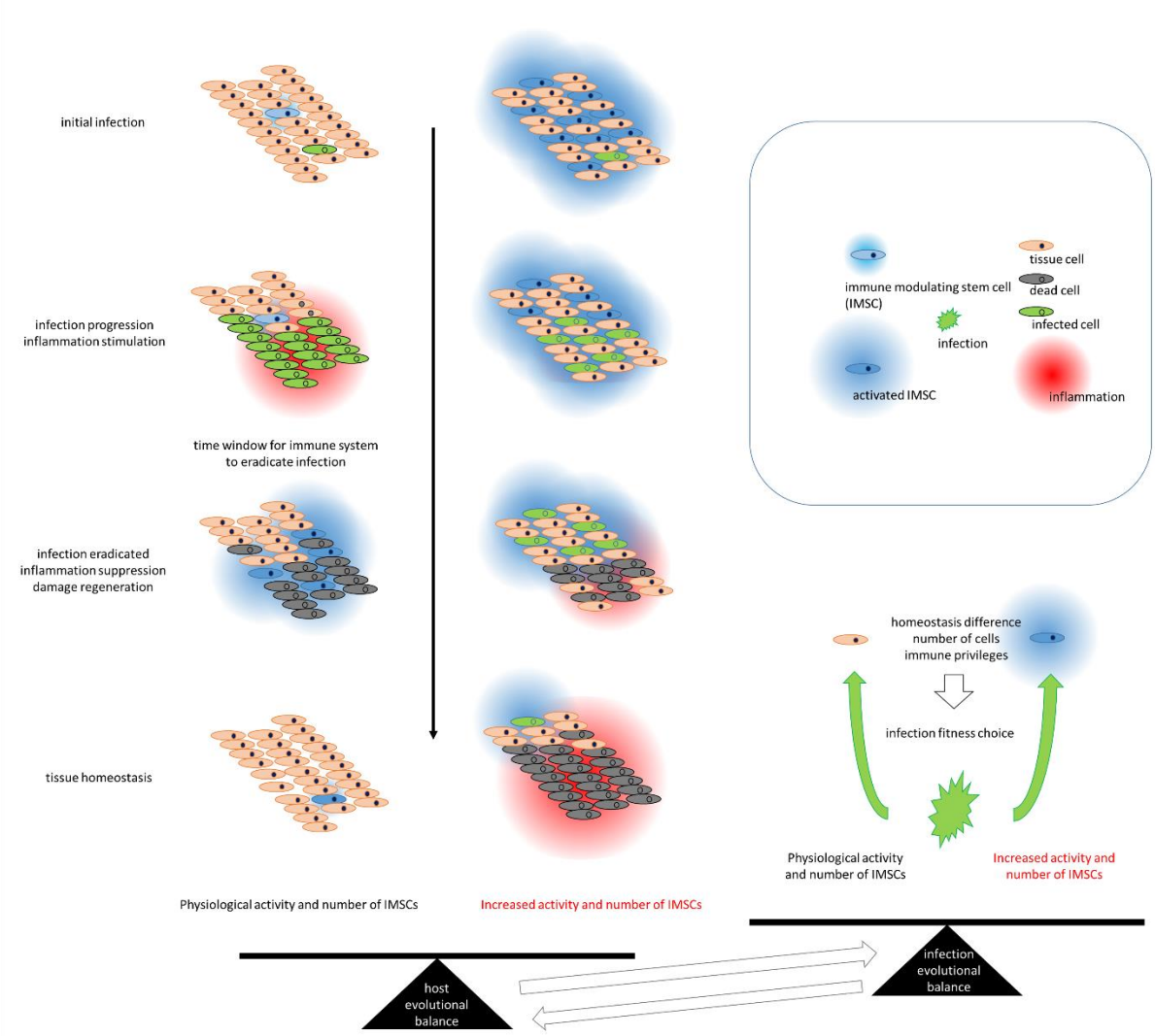

Figure 1. **The evolutionary regulation of immune-modulating stem cell activity and numbers according to their role within the immune system.**

Given that IMSCs provide immune suppression upon activation [27,29,31], it is imperative that stem cells remain inactive. Otherwise, their immune suppression could potentially compromise the immune protection of tissue from invading pathogens. This rationale can also be applied to the presence of a limited number of IMSCs in the tissues of adult organisms, as a higher concentration of IMSCs results in a more pronounced suppression of the immune system (Figure 1). In this manner, IMSCs serve as an activating special agent in the peripheral region, thereby suppressing the potentially destructive actions of an overactive immune system. This model offers an evolutionary rationale for the maintenance of IMSC quiescence and their low prevalence. The traumas and infections have higher risks during life than cancer, so provide

possibly stronger selective pressure for long term living strategies and stay actual for even short term living strategies.

In the event of infection, resident cells signal to attract immune cells. It is noteworthy that MSCs are among the cells that signal for immune activation [30,37]. The relatively limited number of IMSCs induce suppressing signals at a slower rate than the initial proinflammatory reaction. This allows the necessary time for an acute inflammatory reaction to occur (Figure 1). Upon activation, IMSCs migrate to sites of damage [17,19,38,39], where they exert their immunosuppressive effects. Over time, the inflammatory response stimulates the stem system, thereby inducing its regenerative and anti-inflammatory functions. As a result, the initially inflamed area becomes an area of active regeneration, with the inflammatory response polarized towards a regenerative subtype.

The potential for immune suppression functions to be exploited by invading pathogens and oncogenesis has been demonstrated in numerous studies [37,40–43]. That way immune suppression should be presented by complex and enigmatic regulation, which serves as a natural barrier against hijacking. Furthermore, the regulatory mechanisms must be robust. A desired target for infections would be an active immune suppression function in most cells. The additional protection is provided by a strong connection of this function to a small subpopulation of IMSCs. If pathogens target IMSCs and their immunosuppression, it would be necessary for infection to evolve in order to fit the specific conditions of the stem niche. The physiology and energy exchange of stem cells enable their survival and resistance to infection [44,45]. The fitness of a pathogen to a small subgroup would render it ineffective for the infection of other cells, thereby exerting selection pressure against such fitness (Figure 1). This provides an additional rationale for maintaining a low number of IMSCs. The isolation of immune suppression to a small, specific subpopulation of stem cells provides a robust form of protection from infection. The coevolution of immune regulation and infection represents a dynamic and interdependent relationship [40]. It is important to note that IMSCs do lack absolute protection and may be susceptible to infection [37,43].

This model also provides a rationale for the seeding of IMSCs to developing tissues during the stages of embryogenesis [5]. The functional rationale for differentiating between stem cells in adult and embryonic contexts may be attributed to the heightened risk of pathogen invasion in adult tissues during the lifespan. Given the pivotal role of IMSCs in immune function, the divergence in immune status preceding and following labor may provide a potential explanation for the evolutionary adaptation.

The metabolic differences that distinguish stem cells enable them to survive in conditions that would otherwise be lethal for the majority of other cells [15,44]. This enables the regeneration of severely damaged tissues. The acceptance of the model, which posits that stem cells possess pronounced immune privileges, implies the existence of an additional potential for the restoration of areas afflicted by excessive inflammation. Given that disparate physiology and a paucity of IMSCs afford evolutionary protection from infection, the risk associated with migration of IMSCs to contaminated tissue is diminished.

The model proposes an evolutionary perspective for IMSCs, including those of the MSC type, which have been identified in various tissues of the human body [46]. MUSE and VSELs are also stem cells with pronounced immune modulation, derived from a mesenchymal subpopulation of different organs [24,47,48]. The similarities of functions and molecular mechanisms with other quiescent and immune-privileged stem cells, such as hair follicle stem cells, muscle stem cells or hematopoietic stem cells, require further definition [22,23]. It should

be noted that the proposed model does not align with the organizational structure of all tissues and their stem cells. It should be noted that there are examples of stem cell organizations that do not align with the proposed model and that may require significant adjustments [49]. The esophageal epithelium serves as an illustrative example of a tissue wherein 65% of cells are engaged in proliferation, self-maintaince, and repair-related processes, thereby fulfilling the functions typically associated with stem cells within the tissue [50]. $Lgr5^+$ stem cells of the colon and small intestine demonstrate sustained proliferative activity throughout the lifespan [51–53]. These cycling stem cells illustrate disparate evolutionary solutions for tissue-specific mutational processes, in addition to quiescence, which serves as a protective mechanism against mutations [54]. Proliferating $Lgr5^+$ stem cells do not exhibit the same immune privileges as a subpopulation of quiescent $Lgr5^+$ stem cells [22]. In this manner, the cells also exhibit disparate patterns of immune regulation. The regeneration of acute liver damage is mediated by hepatocytes and biliary epithelial cells. In the context of liver homeostasis, hepatocytes and biliary epithelial cells are in a state of quiescence, yet they undergo activation in response to an acute damage event [55]. They are differentiated parenchymal cells of the liver and are the primary contributors to cellular restoration [56,57]. Wound regeneration or inflammation not only activates quiescent cells, but also upregulates dedifferentiation [58]. Dedifferentiation may serve as a means of regulating the stem cell pool [59]. The number of stem cells is also subject to negative feedback, whereby stem cells inhibit dedifferentiation and reduce the number of surrounding stem cells [60,61]. Further studies are required to elucidate the role of dedifferentiation in immune and stem cell regulation. Further experimental study is required to elucidate the strong functional distinction of quiescent, immune-privileged stem cells. Further experimentation is required to elucidate the nuances of immune modulation function across stem cells derived from disparate tissues.

The model provides a logical explanation for the immunomodulating properties of IMSCs that have been applied in clinical practice to protect tissues from pathological inflammation and cytotoxic immune action [24,27,29,62–64]. The model could be extended to elucidate the immune privileges of cancer stem cells as an attribute of the stem state [41,42]. The model can also elucidate the role of non-cancerous stroma in the protection of cancer cells by conceptualizing cancerous tissue as a region of active regeneration, wherein the immunomodulatory function of the stem system is activated [58,65,66]. This provides a natural explanation for the stimulation of immune modulation from non-cancer stroma in response to therapy that damages cancer tissue, thereby further stimulating the function of regeneration [67,68]. The immunomodulating properties of MSCs are significant and well recognized in the scientific community [27,29,62,64]. The principal objective of this article is to designate MSCs or IMSCs as a component of the immune system. It is proposed that IMSCs should be acknowledged as part of the immune system, with a role in the peripheral control of inflammation and autoimmunity, in addition to IMSCs regenerative potential.

The proposed model establishes a functional link between the attributes of IMSCs and their associated immune privileges and immune modulation. The model provides a functional analysis, eschewing a detailed examination of the underlying mechanisms. A particular mechanism may contribute to different functions simultaneously, thereby forming a complex network. However, it should also exhibit functional robustness beyond this. Additional restrictions imposed on IMSC attributes enhance the overall robustness and offer a compelling explanation for their observed values. In order to provide a rationale for the links in the model, I present an evolutionary perspective, but with the support of experimental data that is not necessarily context-specific to evolutionary theory. Nevertheless, the existing deep mutual

integration of immune and stem functions provides a robust foundation for the model. It is important to note that the evolutionary link between functions is not necessarily realized by an actual molecular mechanism. Alternatively, it could be adjusted by independent shifts, which would provide advantages in subsequent generations. The model proposes evolutionary links for the aforementioned attributes. This presentation does not provide a detailed account of the evolutionary process that led to this state or an exhaustive analysis of the specific mechanisms involved. Nevertheless, these issues warrant further investigation.

FUNDING

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

CONFLICT OF INTEREST

The author declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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