Tuberculosis xxx (2016) 1–8

Contents lists available at ScienceDirect

Tuberculosis

journal homepage: http://intl.elsevierhealth.com/journals/tube

Emerging role of mesenchymal stem cells during tuberculosis: The fifth element in cell mediated immunity

Arshad Khan, Robert L. Hunter, Chinnaswamy Jagannath*

Dept of Pathology and Laboratory Medicine, University of Texas McGovern Medical School, Houston, TX, USA

Keywords:
Mesenchymal stem cells
Mycobacterium tuberculosis
Dormancy
Tuberculosis
Autophagy
Nitric oxide
Chemokines
Cytokines
Immunopathology

S U M M A R Y

Mesenchymal stem cells (MSCs) are non-hematopoietic cells that occur in almost all human tissues and can be cultured and expanded to large numbers *in vitro*. They secrete growth factors, cytokines, and chemokines and express Toll-like receptors on their surface, although multiple cell biological mechanisms remain unclear. MSCs are multi-potent and can differentiate into many cell types including adipocytes, neuronal cells and osteoclasts. Despite gaps in cell biology, because of their immunomodulatory and regenerative capacity, several hundred clinical trials have used MSCs for therapy of cancer, autoimmune diseases and control of inflammation during organ transplantation. MSCs secrete immunemodulatory factors and are able to skew T cell responses and shift M1 to M2 differentiation of macrophages. We review the emerging role of MSCs to act as phagocytes for *Mycobacterium tuberculosis* and its role during the persistence of *M. tuberculosis* and spread of infection. Paradoxically, MSCs use innate defense mechanisms of autophagy and nitric oxide to inhibit the growth of intracellular *M. tuberculosis*. In addition, transplantation with autologous MSCs improved the clinical condition of patients with multidrug resistant tuberculosis. Thus, in addition to the well-known immune defense played by macrophages, DCs, classical T cells and non-classical immune cells, MSCs have emerged as a fifth element capable of regulating immune responses during tuberculosis. We discuss their immunomodulatory properties and innate defense mechanisms in the context of developing immunotherapeutic strategies for tuberculosis.

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1. Introduction

Tuberculosis is one of the most ancient and devastating diseases known to mankind and still causes high mortality in modern world, despite widespread primary vaccination with BCG and effective drugs regimen available for susceptible *Mycobacterium tuberculosis* (Mtb) strains. Tuberculosis is a leading cause of death due to infections claiming 1.5 million lives in 2014, even after a 47% reduction in TB mortality since 1990 [1]. Although lung and systemic disease occurs only in 1 out of 10 individuals exposed via aerosol, more than 9 million active tuberculosis cases were reported in 2014. Interestingly, majority of these individuals, who die after developing tuberculosis, are immunocompetent, and many had received childhood vaccination with BCG or anti-tuberculosis treatment.

A major evasion strategy of Mtb is its ability to persist in the host for long periods of time, not only during noncontagious latent tuberculosis infection (LTBI), but also following anti-tuberculosis therapy [2–5]. While a complex array of mechanisms facilitate persistence of Mtb, tuberculosis pathogenesis has been investigated mostly using animal models while the natural course of infection in humans still remains unclear. Tuberculosis is essentially an aerosol induced disease, and blocking transmission has been thought to be a critical step in its prevention. Likewise, prevention of active tuberculosis cases from a latent population is also critical. However, these strategies require an understanding of the interaction of Mtb with host cells during its entry, persistence, dissemination and host defense mechanisms that restrict the pathogen. Studies using various animal models and humans with tuberculosis indicate that, following aerosol infection, Mtb encounters alveolar macrophages of lungs, which are often able to kill them through their innate defense mechanisms. However, in some humans, Mtb survives the initial intracellular encounter with alveolar macrophages and infects the macrophages residing

* Corresponding author. MSB 2.200, Dept. of Pathology and Laboratory Medicine, University of Texas Health Sciences Center, Houston, TX, 77030, USA. Fax: +1 713 500 0730.
E-mail address: Chinnaswamy.jagannath@uth.tmc.edu (C. Jagannath).

http://dx.doi.org/10.1016/j.tube.2016.09.019
1472-9792/Published by Elsevier Ltd.

in the lungs. Cytokine and chemokine signaling from tissue resident macrophages then lead to recruitment of additional host cells, including blood derived monocytes, T cells, neutrophils and dendritic cells (DCs), which help in initiating the adaptive immunity [6–9]. Two possible outcomes that can occur at this stage is either progressive disease or a containment of infection through induction of adaptive immune response. One key feature of an adaptive immune response to tuberculosis, is the formation of granulomas, which are organized cellular structures that contain a central zone of macrophages with persisting or replicating Mtb [9–11]. Although, formation of granuloma is a key event preventing the spread of infection and inflammation that can damage the tissues, Mtb may not be completely killed within granuloma lesions. Indeed, studies show that Mtb bacilli can survive in a dormant stage at the center of the lesion, which is rich in highly differentiated cells such as epithelioid cells, foamy macrophages and multinucleate giant cells (MNGCs) [12]. These are surrounded by a rim of lymphocytes and other immune elements. Macrophages that differentiate into lipid rich foam cells or those which fuse to become MNGCs act as host cells where Mtb can persist in a dormant state. Previous studies also show that T cells and differentiated macrophages also contribute to tissue pathology leading to cavitation and release of infectious bacilli [12,13]. Since the reactivation of dormant Mtb bacilli and subsequent disease development occurs in about 10% of Mtb infected individuals, it remains unclear how MNGCs and foam cells can harbor the dormant bacilli in 90% of latently infected individuals who do not develop disease. Since MNGCs and foam cells may not survive for prolonged periods, perhaps other immune cells provide a niche for persisting and dormant Mtb. Recent studies show that, in addition to the multiple cell types which enrich granulomas, bone marrow derived mesenchymal stem cells (MSCs) seem to populate the periphery of these lesions. Interestingly, both animal and human studies demonstrate that MSCs are emerging as a new niche for the uptake and persistence of Mtb bacilli [14–17]. MSCs are an intriguing source of immune cells since they can be indefinitely replenished from bone marrow, thus providing an uninterrupted source for homing to granulomas during the pathogenesis of tuberculosis [18]. MSCs can be purified from bone marrow and expanded in large numbers using *in vitro* cell culture, and thus have been used in numerous clinical trials to treat cancer, autoimmunity neuronal and inflammatory disorders [19–22]. However, despite extensive clinical usage, the cell biology of MSCs remains poorly understood, particularly in the context of tuberculosis.

2. Regulation of inflammation by MSCs

Source and Differentiation. MSCs that are also known as multipotent stromal cells, possess stem cell-like characteristics including multi-potency, self-renewal and differentiation, and can be isolated from a variety of different sources such as bone marrow, muscle, adipose tissue, deciduous teeth, skin, Wharton's jelly of umbilical cord, umbilical cord blood, peripheral blood, and others [23–27]. MSCs adhere to plastic surface and using specific growth factors and pharmacological agents, they can differentiate into multiple cell lineages, including adipocytes, chondrocytes, myocytes, osteoblasts, epithelial cells, glial cells, neuronal cells, tenocytes, hepatocytes, and islet cells. Multiple surface markers including CD73, CD90, and CD105 are used to identify them although an exclusive marker has not been found. MSCs are considered cells of non-hematopoietic origin and can be distinguished from other cells by their inability to express hematopoietic surface markers such as CD11, CD14, CD34, CD45, and HLA-DR. Although, their anatomical localization and functional role in different adult and fetal tissues are still being uncovered, MSCs have an immunomodulatory function, and regenerative capacity helping the maintenance of organ function through tissue repair. It is well recognized that MSCs have the ability to differentiate depending upon the microenvironment niche; thus they can differentiate into fibroblasts in the skin, astrocytes in the central nervous system, stromal cells in the bone marrow, adipocytes in the fat tissue, osteocytes in the bone, chondrocytes in the cartilage and monocytes in muscles [22]. Due to continuous replenishment for the bone marrow, ability to render immune-modulation, secrete cytokines and growth factors that help in regeneration, MSCs are able to replace dead or dysfunctional cells and tissues that are lost through normal aging, disease or injury [28,29].

Three physiological functions and regulation of tissue repair. The immunomodulatory effect of MSCs is exerted through a concerted effect of multiple cytokines, chemokines and oxidants like Nitric Oxide (NO), prostaglandin E2 (PGE2), indoleamine 2, 3-dioxygenase (IDO), hepatocyte growth factor (HGF) and transforming growth factor (TGF)-β [30]. Through these soluble factors, MSCs are able to suppress the proliferation and functions of $CD4^+$ (TH1 as well as TH17 cells), $CD8^+$ T cells, and natural killer cells to keep the inflammation under control at the site of repair [25,30,31]. Furthermore, cytokines and chemokines secreted by MSCs may also promote the expansion and inhibitory function of regulatory T cells thereby controlling the inflammation [32].

The regenerative properties of MSCs are mediated through the secretion of several growth factors in combination with some chemokines that induce cell proliferation and angiogenesis. MSCs are known to express mitogenic proteins such as transforming growth factor-alpha (TGF-α), epithelial growth factor (EGF), TGF-β, HGF, basic fibroblast growth factor (FGF-2) and insulin-like growth factor-1 (IGF-1), to escalate fibroblast, endothelial and epithelial cell division [33,34]. Studies also show that vascular endothelial growth factor (VEGF), IGF-1, EGF and angiopoietin-1 is also released by MSCs that help in recruitment of endothelial lineage cells and initiation of vascularization [35,36]. These multiple growth factors, in concert with many other soluble mediators promote angiogenesis, regeneration, remodeling, immune cell activation or suppression, and cellular recruitment during tissue repair. The repair process also involves regulating extracellular matrix deposition, collagen synthesis, fibroblast proliferation, platelet activation and fibrinolysis via combination of growth factors, in a milieu specific manner, to further facilitate the trophic properties of MSCs [37].

3. Regulation of inflammation during infection by MSCs

Many studies show that during infection, immune activation can lead to tissue damage and MSCs can play a role because of their trophic and immunosuppressive properties [36,37]. Although, mechanisms of homing are not clear, and almost certainly chemokines and chemokine receptors are involved, many studies show migration of MSCs to inflamed tissue [36,38,39]. Since inflammation is common during infections, MSCs can play a regulatory role during infectious diseases. Thus, MSCs can sense and respond to chemotactic signals sent by infected and inflamed cells. Direct contact with pathogens is also known to alter their secreted products, migration, proliferation, differentiation and immunomodulatory properties [40]. A recent review outlines the multiple mechanisms through which MSCs can affect both infection and inflammation [41]. Essentially, the mechanisms seem to involve an interplay between, Toll-like receptors (TLRs) expressed on the surface of MSCs, cytokines and chemokines, macrophages, DCs and multiple subsets of T cells. During an infection, it is well-established that macrophages and DCs recognize pathogens through their TLRs

Please cite this article in press as: Khan A, et al., Emerging role of mesenchymal stem cells during tuberculosis: The fifth element in cell mediated immunity, Tuberculosis (2016), http://dx.doi.org/10.1016/j.tube.2016.09.019