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Mesenchymal Stem Cells: The New Players in the Pathogenesis of Tuberculosis

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Tuberculosis (TB) is the most common and deadly infectious disease associated with significant mortality and morbidity [1,2]. TB is the second highest cause of mortality from an infectious agent accounting for 2 million deaths each year [3]. There are more than 9 million new cases of TB every year worldwide, and incidence is declining only at a rate of less than 1% per year [4]. *Mycobacterium tuberculosis (M. tb)* is the causative agent of TB, which is transmitted through aerosol droplets that are inhaled by the host and deposited in the lung which become the reservoir of infection [5-7]. A recent surge in the antibiotic resistant strains of *M. tb* has further complicated the treatment of this deadly disease [8-11]. Lack of understanding about the pathogenesis of the disease has hindered the development of effective preventive strategies against this fatal disease.

Raghuvanshi et al. [12] recently reported that Mesenchymal stem cells (MSCs) play a crucial role in ability of *M. tb* to evade potent host immune responses and cause TB. MSCs are multipotent stem cells that can differentiate into a variety of cell types, including osteoblasts (bone cells), chondrocytes (cartilage cells) and adipocytes (fat cells) [13-15]. Employing a mouse model of *M. tb* infection, these workers demonstrated that splenocytes from these infected mice show profoundly reduced proliferation in response to the T cell mitogen Con A indicating immune suppression. Using a series of experiments these workers confirmed that inhibition of T cells is mediated by accessory cells and not restricted to polyclonal activation of T cells. These workers identified that majority of these accessory cells express stem cell antigen Sca-1 that is characteristic of the stem cell lineage. These cells also express CD29, CD44, and Flk-1 but did not express CD34, CD45, CD11b, CD11c and Gr1 that are the signature membrane markers of MSCs. In addition these cells readily differentiate into adipocytes confirming their identity as bonafide MSCs. To further confirm the role of MSCs in the pathogenesis of TB, these workers reconstituted TGFβRIIDN mice, that are resistant to *M. tb* infection, with MSCs isolated from infected mice and then infected with *M. tb*. Interestingly reconstituted TGFβRIIDN mice were susceptible to *M. tb* infection whereas control TGFβRIIDN animals that did not receive any cells or received adherent spleen cells did not get TB. MSCs were observed to surround the *M. tb* organisms, which might help in confining them within granuloma like structures. At par with these observations in mouse model, these workers also demonstrated that MSCs surround granuloma of human patients with TB.

Another intriguing finding that these workers observed during this study is that nitric oxide (NO) plays an important role in the recruitment of these MSCs at the site of granulomas. However immune suppression mediated by these MSCs was independent of IL-6 as addition of anti-IL-6 was unable to overcome the blockade in splenocyte proliferation. MSCs have earlier been shown to play an important role in the regulation of immune responses in Crohn's disease, and in tumors by migrating to the inflammation sites [16-21] but so far their role in TB has not been elucidated. This study by Raghuvanshi et al. [12] is the first novel observation that MSCs play a detrimental role in the pathogenesis of TB.

In summary these workers observed that "large numbers of MSCs infiltrate into the site of tuberculosis infection and position themselves between the harbored pathogens and effector T cells that target the pathogens". These workers concluded that "MSCs inhibit cellular immune responses, which contributes to the establishment of persistent *M. tb* infection". These interesting findings reported by the team of Gobardhan Das will definitely open up avenues for the treatment of TB, which affects about one third of the human population. The recruitment of MSCs create immunosuppressive environment by preventing proliferation of T cells hence preventing the killing of *M. tb* by these potent immune cells. Therefore targeting MSCs or NO seems a plausible therapeutic intervention for the design of new effective preventive strategies against TB.

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