Mesenchymal Stem/Stromal Cells (MSCs): Role as Guardians of Inflammation

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Recent observations have demonstrated that one of the functions of mesenchymal stem/stromal cells (MSCs) is to serve as guardians against excessive inflammatory responses. One mode of action of the cells is that they are activated to express the interleukin (IL)-1 receptor antagonist. A second mode of action is to create a negative feedback loop in which tumor necrosis factor-α (TNF-α) and other proinflammatory cytokines from resident macrophages activate MSCs to secrete the multifunctional anti-inflammatory protein TNF-α stimulated gene/protein 6 (TSG-6). The TSG-6 then reduces nuclear factor-κB (NF-κB) signaling in the resident macrophages and thereby modulates the cascade of proinflammatory cytokines. A third mode of action is to create a second negative feedback loop whereby lipopolysaccharide, TNF-α, nitric oxide, and perhaps other damage-associated molecular patterns (DAMPs) from injured tissues and macrophages activate MSCs to secrete prostaglandin E_2 (PGE_2). The PGE_2 converts macrophages to the phenotype that secretes IL-10. There are also suggestions that MSCs may produce anti-inflammatory effects through additional modes of action including activation to express the antireactive oxygen species protein stanniocalcin-1.

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We and other vertebrates are equipped to live in a sea of microorganisms. The reason we survive is because we have formidable inflammatory and immune response systems to protect us against both external confrontations with microorganisms and internal confrontations with the bacteria in our intestinal flora that outnumber the cells in our bodies.[1,2] However, the same systems need multiple checks to protect us against excessive inflammatory and immune responses. In fact, there is an increasing realization that excessive or nonresolving inflammation makes a major contribution to the damage wrought by diseases such as obesity, diabetes, myocardial infarction (MI), stroke, parkinsonism, and Alzheimer's disease.[3,4] Fortunately, we have multiple systems for resolving and modulating inflammation. The systems include small molecules such as prostaglandins, lipoxins, protectins, and resolvins.[5] They also include cellular phenotypes such as alternatively activated M2 macrophages[6] and regulatory T cells.[7,8] Recent reports indicate that additional important guardian cells for modulating inflammation are mesenchymal stem/stromal cells (MSCs). The interest in the guardian role of MSCs is in part related to their presence as adventitial reticular cells[9] that participate in normal wound repair and in regulation of hematopoietic cells in bone marrow.[10] The interest in MSCs has been further enhanced by their potential use for therapies of various diseases, because the cells can be readily obtained from patients, they are easily expanded in culture, and they are generally not tumorigenic. Recent reports have demonstrated that many, but not all, of the therapeutic effects of the cells seen in animal models are explained by MSCs being activated by signals from injured tissues to secrete anti-inflammatory factors. In some instances, direct administration of the same factors replicates the anti-inflammatory effects of the MSCs. Therefore, the factors secreted by activated MSCs may replace the use of the cells for some therapeutic applications.

CHANGING PARADIGMS IN RESEARCH ON MSCS

The role of MSCs as guardians of inflammation has gradually emerged from research on the cells over the past several decades. The evolving data have prompted dramatic shifts in the hypotheses or paradigms for the research.[11] Initially, the cells were explored as feeder layers that provided a niche for culture of hematopoietic cells (paradigm I). Then the cells were explored as reparative cells that can engraft in injured tissues and differentiate to replace damaged cells (paradigm II). More recently, the data demonstrate that the cells only transiently appear in injured tissues under most conditions, but during their brief appearance they respond to crosstalk with injured cells to limit tissue destruction or enhance repair by a variety of mechanisms (paradigm III). The mechanisms include (a) upregulation of genes that modulate excessive inflammatory and immune reactions; (b) providing a niche to enhance proliferation and differentiation of tissue-endogenous stem/progenitor cells (as in paradigm I); and (c) transfer of vesicular components that contain mitochondria and microRNAs.

The role of MSCs as guardians of inflammation became more apparent as the events initiating inflammation have been defined in greater detail.[4,12–14] The events include (a) both passive and active release from injured cells or macrophages of intracellular cytokines such as interleukin (IL)-1α that stimulate parenchymal cells to produce chemokines that recruit neutrophils; (b) classical

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activation of resident macrophages by damage-associated molecular patterns (DAMPs) or pathogen-associated molecular patterns (PAMPs) that interact with pattern recognition receptors to produce high levels of proinflammatory cytokines as well as reactive nitrogen and reactive oxygen species that induce the acute phase response of inflammation.

The literature on the anti-inflammatory effects of MSCs is continuing to expand at a rapid rate with over 500 entries in PubMed under "MSCs and inflammation." We are unable to review all the entries in detail, and therefore we elected to focus here on several examples in which the anti-inflammatory effects of MSCs appear to be best explained at the cellular and molecular levels. The examples deal with inflammation of tissues as a discrete process and not as a component of adaptive immunity, a topic that has been covered in other recent reviews.[15–18]

ANTI-INFLAMMATORY EFFECTS OF MSCS IN A MODEL OF LUNG INJURY

One series of experiments were with a model of bleomycin-induced lung injury.[19,20] In the model, intravenous (i.v.) infusion of minimally expanded murine bone marrow-derived MSCs (500,000 cells per mouse) decreased the inflammatory response to bleomycin and prevented the lungs from developing fibrosis.[19,20] The beneficial effects of the MSCs were largely explained by the cells being activated to secrete IL-1 receptor antagonist (IL-1ra). The MSCs were effective only when administered at the same time as the bleomycin and not at later time points. This observation suggests that the action of MSCs in this model was exerted in the initial phases of the injury in which there is extensive apoptosis of macrophages.[21] The observations were consistent with demonstrations that the IL-1 pathway plays a central role in the generation of sterile inflammation,[13,22] and its effects are similar to the effects of tumor necrosis factor-α (TNF-α) in infectious inflammation.[4,12,23] Both human and mouse MSCs from the bone marrow express high levels of IL-1ra,[19] and experiments in culture demonstrated that IL-1ra secreted from MSCs inhibited the production of TNF-α by IL-1α-activated macrophages (RAW 264.7). However, infusion of MSCs in the mouse model of bleomycin-induced lung injury was more effective than recombinant or virally delivered IL-1ra. The results indicated that one way in which MSCs can modulate the early phases of inflammation is to secrete IL-1ra and thereby blunt the effects of IL-1 and TNF-α in stimulating both sterile and infectious inflammation.[23] An analogous mechanism was provided by the observation[24] that human MSCs (hMSCs) attenuated systemic inflammation in mice after intraperitoneal (i.p.) injection of lipopolysaccharide by secreting soluble receptor-1 for TNF (sTNFR1), which binds to TNF-α and neutralizes the activity of the cytokine.

ANTI-INFLAMMATORY EFFECTS OF HMSCS IN A MODEL OF MI

One of the paradoxical observations with MSCs is that i.v. infusions of MSCs produced beneficial effects in repairing tissues in distal organs such as heart, pancreas, brain, and spinal column even though most i.v. infused MSCs are trapped in the lung.[11] The paradox was at least in part resolved by experiments with hMSCs were infused i.v. in a mouse model for MI.[25] The i.v. injection of hMSCs (2×10^6 cells per mouse) significantly reduced the early inflammatory response to permanent ligation of the anterior descending coronary artery and subsequently reduced the size of the myocardial infarcts. Also, significant improvement was observed in the function of the left ventricle as assayed by echocardiography 3 weeks later. However, quantitative assays for human Alu sequences and human mRNA for GAPDH as a measure for live hMSCs indicated that only a small fraction of the infused MSCs were recovered in the heart after injection. Also, the appearance of the hMSCs in the heart was transient: about 1,500 of the 2×10^6 were present at 24 hours, and they disappeared by 48 hours. Most of the injected cells were found trapped in the lungs as microemboli[25,26] and they disappeared with a half-life of 24 hours. In an attempt to explain the beneficial effects of the MSCs, RNA was extracted from lungs of the mice 10 hours after infusion of the hMSCs and was assayed on human microarrays. After filtering for cross hybridization with mouse RNAs, the data indicated that the hMSCs trapped in the lungs as microemboli were activated to upregulate the expression of over 50 human genes. Among the upregulated genes, the most interesting was the gene for the multipotent anti-inflammatory protein referred to as TNF-α stimulated gene/protein 6 (TSG-6). The hMSCs with an siRNA knockdown of the *TSG-6* gene had little or no effect in the MI model. Also, the i.v. administration of recombinant human TSG-6 (rhTSG-6) had about the same beneficial effect as hMSCs. The results were explained by a sequence in which the hMSCs were activated by being trapped as microemboli to secrete TSG-6, and the TSG-6 decreased the early and excessive inflammatory response in the heart that causes destruction of cardiac tissue (**Figure 1**). In effect, by being activated to secrete TSG-6, the MSCs acted at a distance to reduce injury to the heart.

ANTI-INFLAMMATORY EFFECTS OF hMSCS AND rhTSG-6 IN A MODEL OF CORNEAL INJURY

I.v. administration of hMSCs was also shown to act at a distance to reduce inflammation in a model of sterile injury to the cornea in rats. The corneas were injured by brief exposure to alcohol followed by mechanical scrapping of the epithelium and limbus that removed the stem cells found in the limbus. i.v. infused hMSCs (1×10^7 cells per rat) markedly decreased neutrophil infiltration, production of proinflammatory cytokines, and development of the opacity in the cornea.[27] Surprisingly, i.p. infusion of the hMSCs was also effective in suppressing inflammation and preventing the opacity in the cornea. A quantitative assay for human mRNA for GAPDH demonstrated that <10 hMSCs were present in the corneas of rats 1 day and 3 days after i.v. or i.p. administration of 1×10^7 hMSCs. However, the hMSCs with an siRNA knockdown of the *TSG-6* gene were not effective. Also, the beneficial effects of hMSCs were largely duplicated by i.v. administration of rhTSG-6. Therefore, the data demonstrated that systemically administered hMSCs reduced inflammatory damage to the cornea without engraftment in the tissue and that the anti-inflammatory effects of the cells were probably explained by their secretion of TSG-6.

A related series of experiments demonstrated that direct injection of rhTSG-6 into the anterior chamber of the rat eye also decreased excessive inflammation in injured cornea. The anti-inflammatory effects of the rhTSG-6 were dose-dependent (**Figure 2**).[28] The effective suppression of excessive inflammation

in the early phase of injury subsequently led to a marked decrease in development of blinding opacity and neovascularization of the cornea at day 21 of injury.

These data collectively indicate that MSCs effectively protect the heart or cornea from injury and promote tissue regeneration by modulating acute excessive inflammation primarily by secreting TSG-6.

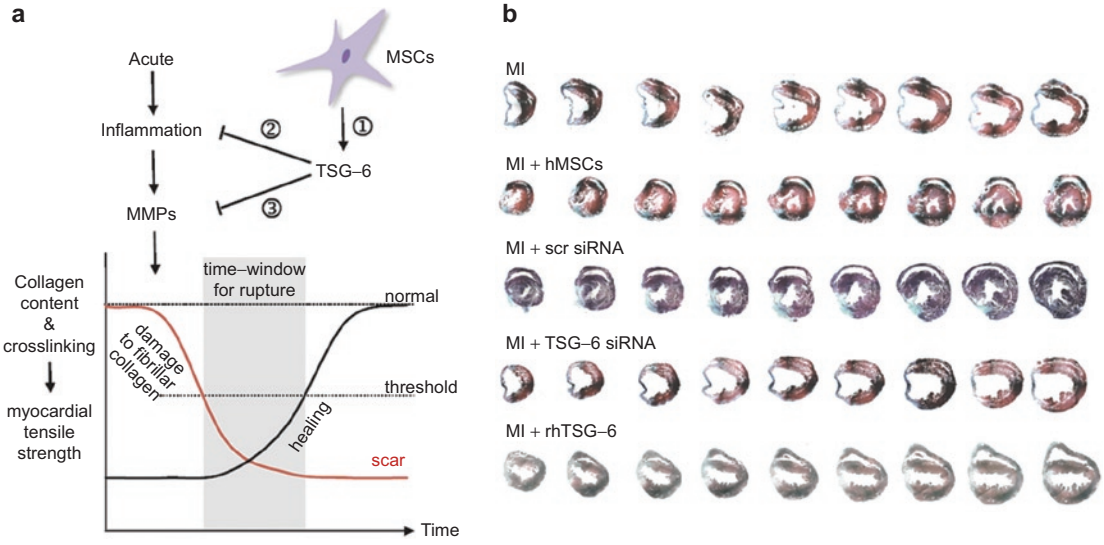

Figure 1 Anti-inflammatory effects of human mesenchymal stem/stromal cells (hMSCs) activated to secrete tumor necrosis factor-α (TNF-α) stimulated gene/protein 6 (TSG-6) in a mouse model of myocardial infarction. (**a**) Schematic diagram. (1) hMSCs injected intravenously were trapped in the lungs and activated to secrete TSG-6 (TNF-α stimulated gene/protein 6). (2) The TSG-6 decreased the normal but excessive inflammatory response that damages the heart. (3) The TSG-6 probably further decreased proteolytic damage to the heart by inhibiting matrix metalloproteinases (MMPs) (see refs. 42,43,46). (**b**) Selected sections through heart. Each heart was cut from apex to base into over 400 sequential 5 µm sections. Every twentieth section is shown. Either hMSCs or hMSCs transduced with the scrambled siRNA (scr siRNA) decreased the size of myocardial infarction examined 3 weeks later. However, hMSCs with an siRNA knockdown of the *TSG-6* gene (TSG-6 siRNA) had no effect on infarct size. Intravenous infusion of 100 µg of recombinant human (rh) TSG-6 immediately following the surgery and at 24 hour also decreased infarct size. (**a**) Reproduced with modifications and with permission from Elsevier.[46] (**b**) Reprinted with permission from Elsevier.[25]

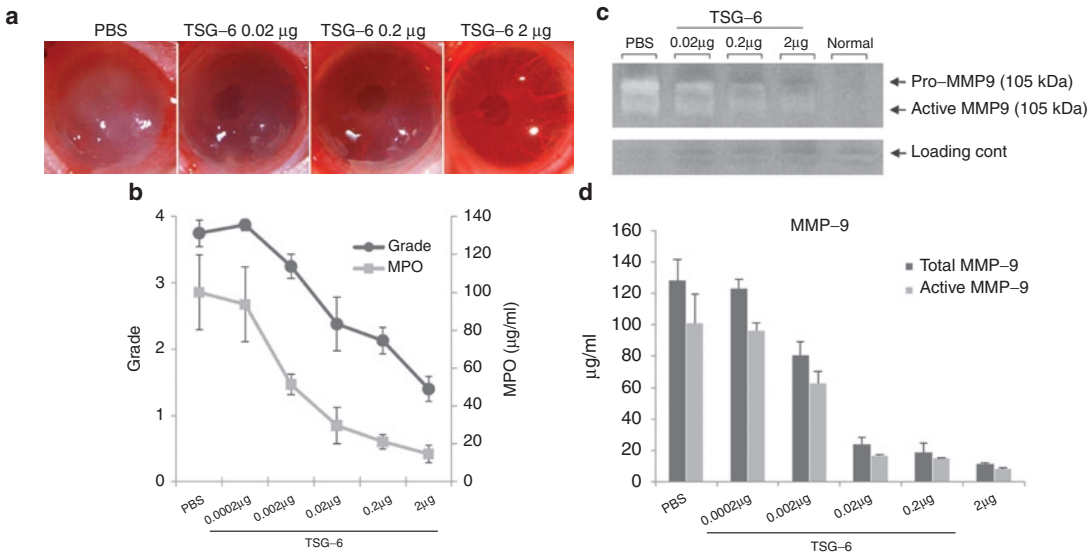

Figure 2 Dose-dependent effects of tumor necrosis factor-α (TNF-α) stimulated gene/protein 6 (TSG-6) in reducing corneal inflammation and opacity. Sterile inflammation was produced in corneas of Lewis rats by brief exposure to 100% ethanol followed by mechanical debridement of the cornea and limbal epithelium that removed the stem cells located in the limbus. (**a**) Representative corneal photographs on day 3 postinjury demonstrated that TSG-6 suppressed development of corneal opacity after chemical injury in a dose-dependent manner. (**b**) The anti-inflammatory effects of TSG-6 were dose-dependent as reflected in clinical grade of corneal opacity and myeloperoxidase (MPO) concentration as a semiquantitative assay of neutrophil infiltration. Values are mean ± SD; $n = 3$ for each group. (**c**) Gelatin zymography of corneas for pro-MMP-9 and active matrix metalloproteinase (MMP)-9. (**d**) Total and active MMP-9 concentration in the cornea as assayed by enzyme-linked immunosorbent assay (ELISA). Values are mean + SD; $n = 5$ for each group. Significant improvements were observed with dose of 0.002 µg but maximal effects were obtained with 2 µg. Reprinted with permission from National Academy of Sciences, USA.[28]

ANTI-INFLAMMATORY EFFECTS OF HMSCS AND rhTSG-6 IN A MODEL FOR PERITONITIS

The anti-inflammatory action of MSCs through secretion of TSG-6 was further demonstrated in a model in which peritonitis was induced in mice by injection of zymosan, a glucan prepared from the cell walls of yeast.[29] After hMSCs (1.6×10^6 cells per mouse) were infused i.p. 15 minutes after zymosan, there was a significantly decrease in neutrophils and monocytes/macrophages in the peritoneal cavity. As in the previous experiments, hMSCs transduced with the TSG-6 siRNA were not effective, and i.p. infusion of 30 µg rhTSG-6 largely reproduced the anti-inflammatory effects of hMSCs. The anti-inflammatory effects of the hMSCs were explained by their effects on resident macrophages, the sentinel cell for inflammatory responses in most tissues.[4,12,14] In cultures of murine macrophages (RAW 264.7) that were stimulated with zymosan, both hMSCs and rhTSG-6 decreased the secretion of the proinflammatory cytokines, TNF-α and IL-1α. They also suppressed the activation and translocation of the nuclear factor-κB (NF-κB) complex to the nucleus. As expected, hMSCs had no significant effect after the *TSG-6* gene was knocked down with an siRNA. The inhibitory effects of hMSCs and TSG-6 were dependent on the expression of CD44, because they did not suppress NF-κB signaling in cells or in transgenic mice that did not express CD44. Zymosan stimulates NF-κB signaling through the Toll-like receptor 2 (TLR2). The inhibitory action of TSG-6 was dependent on the interaction of CD44 with TLR2 and not on the downstream of TLR2 signaling, since TSG-6 did not inhibit the TLR2/NF-κB pathway in cells overexpressing two of TLR adaptor proteins (MyD88 and TIRAP) that interact with the cytoplasmic tail of TLR2. The overall effect was that the hMSCs introduced a negative feedback loop into the inflammatory response (**Figure 3**) in which MSCs and TSG-6 suppressed the initial production of proinflammatory cytokines from zymosan-activated macrophages. They thereby inhibited the amplification of the proinflammatory signals by mesothelial cells that produce high levels of IL-6 and CXCL1 to recruit neutrophils.[29] TLRs on resident macrophage play critical roles in initiating inflammation in most tissues.[4,14,30,31] The negative feedback loop introduced by MSCs and TSG-6 on the TLR2/NF-κB pathway in macrophages may therefore largely account for the beneficial effects of MSCs in other disease models in which excessive inflammatory responses contribute to tissue damage.

ANTI-INFLAMMATORY EFFECTS OF MOUSE MSCS IN A MODEL FOR SEPSIS

A different explanation for the anti-inflammatory effects of MSCs was demonstrated in a mouse model of sepsis produced by cecal ligation and puncture.[32] Németh *et al.* found that there was a significant improvement in the survival of mice that received 1 x 10^6 mouse MSCs (mMSCs) i.v. at the time of surgery, 24 hours before or 1 hour after surgery. Also, the serum levels of TNF-α and IL-6, proinflammatory cytokines that have a central role in sepsis,[33] were significantly reduced by administration of the mMSCs. After i.v. infusion, most of the mMSCs were found in the lungs, and they disappeared over time but few were visible 24 hours after injection. Interestingly, the serum level of IL-10, an anti-inflammatory cytokine secreted by macrophages, was elevated at 6 and 12 hours in mice receiving MSCs. Either depletion of macrophages or administration of blocking antibodies to IL-10 eliminated beneficial effects of MSCs in mice with sepsis. MSCs from IL-$10^{-/-}$ mice were still effective in improving the survival of mice with sepsis. Thus, the data suggested that MSCs were not the source of IL-10 but they ameliorated sepsis by inducing IL-10 production in host macrophages. The MSCs apparently induced the production of IL-10 in the macrophages by secreting nitric oxide, but some of the data suggested that the macrophages also produced nitric oxide. A series of *in vivo* and *in vitro* experiments demonstrated that TLR4 and TNFR-1-mediated activation of NF-κB in the mMSCs upregulated expression of cyclooxygenase-2 and thereby increased secretion of prostaglandin E_2 (PGE_2). PGE_2 in turn bound to EP2 and EP4 receptors on macrophages and changed macrophages to the phenotype that secretes IL-10. The IL-10 produced by host macrophages reduced inflammation in mice with sepsis (**Figure 4**). IL-10 is an essential component of a negative feedback loop in inflammation, because it typically inhibits the response that initiated its own production and acts on macrophages and other cells that produce inflammatory

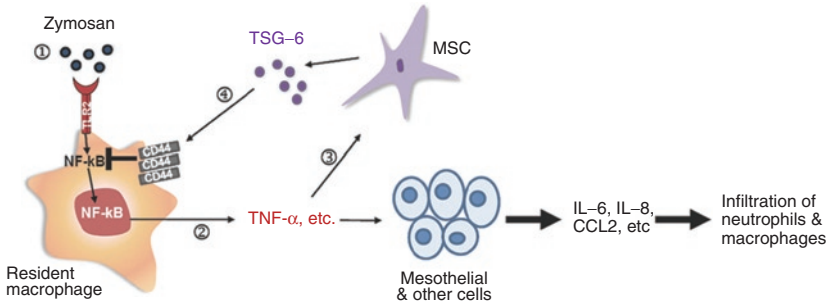

Figure 3 The anti-inflammatory effects of human mesenchymal stem/stromal cells (hMSCs) and tumor necrosis factor-α (TNF-α) stimulated gene/protein 6 (TSG-6) in a mouse model of zymosan-induced peritonitis. (**1**) Zymosan-activated nuclear factor-κB (NF-κB) signaling in resident macrophages via Toll-like receptor 2 (TLR2). (**2**) Activation of the NF-κB signaling pathway increased the production of proinflammatory cytokines to initiate the cascade of proinflammatory cytokines that was amplified by mesothelial cells and other cells of the peritoneum. (**3**) The proinflammatory cytokines also activated the hMSCs to secrete TSG-6. (**4**) TSG-6 decreased TLR2/NF-κB signaling in the resident macrophages through a direct interaction with CD44 or in a complex with hyaluronan. The amplification of the proinflammatory signals by mesothelial cells to recruit neutrophils was modulated by a negative feedback loop introduced by hMSCs and TSG-6. Reprinted with permission from the American Society of Hematology.[29]

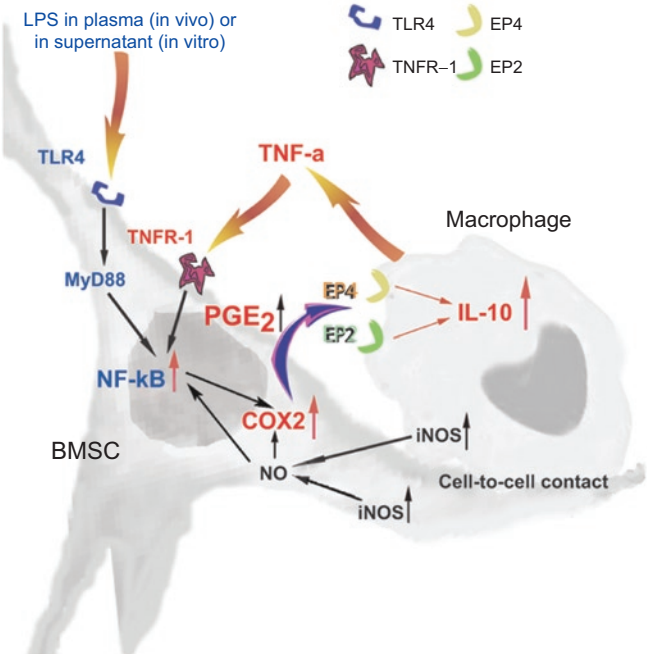

Figure 4 Schematic for the anti-inflammatory effects of mesenchymal stem/stromal cells (MSCs) based on observations in a mouse model for sepsis. Bacterial toxins such as lipopolysaccharide (LPS) and circulating tumor necrosis factor-α (TNF-α) acted on the TLR4 and TNF receptor-1 (TNFR-1) of MSCs to activate the nuclear factor-κB (NF-κB) signaling. Activation of NF-κB signaling upregulated expression of cyclooxygenase-2 (COX2) and the COX2 increased synthesis of prostaglandin E_2 (PGE_2). PGE_2 was secreted and bound to EP2 and EP4 receptors on macrophages. The PGE_2 thereby increased IL-10 secretion by macrophages to reduce the inflammatory response. Reprinted with permission from Macmillan Publishers Ltd.[32]

mediators.[34] The observations by Nemeth *et al.*[32] suggested that MSCs can create another negative feedback loop of inflammation, one that apparently does not involve TSG-6.

One caution about the results[32] was expressed in a subsequent report describing similar experiments with cecal ligation and puncture in mice. Mei *et al.*[35] observed that the mMSCs had beneficial effects but their data indicated a decrease instead of an increase[32] in serum levels of IL-10 that were assayed 24 hours after i.v. infusion of mouse MSCs. There are several possible explanations for the discrepancy, including differences in when the MSCs were infused, in when the serum was assayed, and in the dose of cells administered. Also, Mei *et al.* used mMSCs that were extensively characterized and obtained from an NIH-sponsored core facility (http://medicine.tamhsc.edu/irm/msc-distribution.html). Therefore, they minimized the danger of using mMSCs that are easily transformed by overexpansion in culture.[11,36]

ADDITIONAL OBSERVATIONS THAT MSCS CAN POLARIZE MACROPHAGES TO THE ALTERNATIVELY-ACTIVATED M2 PHENOTYPE

The suggestion by Nemeth *et al.*[32] that MSCs can reprogram macrophages from a proinflammatory M1 phenotype to the alternatively activated or anti-inflammatory M2 phenotype was supported by several other reports. Kim *et al.*[37] found that human macrophages cocultured with human bone marrow-derived MSCs expressed high levels of a marker of alternatively activated M2 macrophages (CD206, a mannose receptor), high levels of IL-10 and IL-6, and low levels of IL-12 and TNF-α. They had increased phagocytic activity. In parallel observations with mouse MSCs, Maggini *et al.*[38] also found that mouse bone marrow-derived MSCs switched macrophages to a regulatory phenotype characterized by decreased expression of inflammatory cytokines, increased phagocytosis of apoptotic cells, and increased susceptibility to infection by intracellular pathogens. The effects were apparently mediated by secretion of PGE_2 by the MSCs since acetylsalicylic acid, a cyclooxygenase inhibitor, impaired the ability of MSCs to change the phenotype of the macrophages. In similar experiments with human gingiva-derived MSCs, Zhang *et al.*[39] also observed that the MSCs or conditioned medium from the MSCs converted macrophages to the M2 phenotype, and apparently because of the conversion, they enhanced wound repair *in vivo*. In addition, they found that the MSCs suppressed TNF-α secretion by macrophages in a manner that correlated with impaired activation of NF-κB p50.

Therefore, there is a large body of evidence that MSCs suppress inflammation and enhance tissue repair by modulating the phenotype of macrophages.

THERAPEUTIC IMPLICATIONS OF THE ANTI-INFLAMMATORY EFFECTS OF MSCS

The observations that many of the anti-inflammatory effects of MSCs can be reproduced by soluble factors the cells produce raise an obvious question: can therapies with the factors replace therapies with MSCs? Several of the factors are not attractive candidates. For example, therapy with recombinant IL-1ra has been introduced into clinical trials. It appears to have limited applications because improvements were seen in a small number of patients with gout,[40] but there was no benefit in patients with osteoarthritis and rheumatoid arthritis.[41] Other factors produced by MSCs, such as nitric oxide, indoleamine dioxygenase, or PGE_2 are not promising candidates because they have short half-lives or they have adverse effects when administered systemically. However, there appear to be adequate reasons for testing the protein TSG-6 for therapeutic uses. The protein was previously shown to have multiple anti-inflammatory effects in addition to its modulation of NF-κB signaling in macrophages[29] without any apparent toxic effects, even in transgenic mice overexpressing the gene.[42,43]

Further examination of the beneficial effects of MSCs in disease models may identify additional factors that can be used therapeutically. Among the factors of therapeutic interest is stanniocalcin-1 that is secreted by MSCs in response to signals from apoptotic cells[44] and that reduces reactive oxygen species by upregulating the expression of uncoupling protein-2 of mitochondria.[45] Since low levels of reactive oxygen species are proinflammatory and high levels are proapoptotic, stanniocalcin-1 may be both anti-inflammatory and antiapoptotic.

CONCLUSION

The role of MSCs as guardians against excessive inflammation explains many of the beneficial effects observed with administration of the cells in animal models for a large number of diseases, including models for lung injury, diabetes, sepsis, MI, sterile injury to the cornea, and stroke. The recent information that has

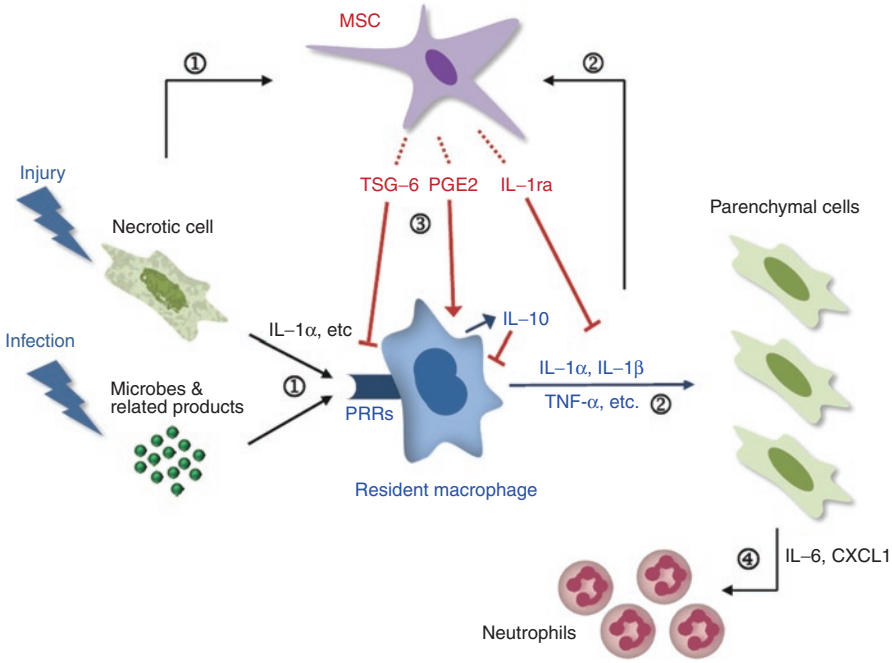

Figure 5 Summary of some of the anti-inflammatory effects of mesenchymal stem/stromal cells (MSCs). (**1**) Damage-associated molecular patterns (DAMPs) and interleukin (IL)-1α released by sterile injury or pathogen-associated molecular patterns (PAMPs) released by infectious injury to tissues activate resident macrophages through receptors involving pattern recognition receptors (PRRs). (**2**) The activated macrophages produce proinflammatory cytokines such as IL-1α, IL-1β, or tumor necrosis factor-α (TNF-α) to initiate the inflammatory cascade. (**3**) Simultaneously, the proinflammatory cytokines and probably other signals from injured cells activate MSCs to secrete anti-inflammatory factors that include TNF-α stimulated gene/protein 6 (TSG-6), PGE_2, and IL-1ra that either modulate the activation of the resident macrophages or decrease the downstream effects of the proinflammatory cytokines. (**4**) The net effect is to decrease the amplification of the proinflammatory signals by parenchymal cells through the secretion of IL-6, CXCL1, and related factors and as a result to decrease the recruitment of neutrophils.

defined the anti-inflammatory factors produced by the cells (summarized in **Figure 5**) opens the possibility of using one or more of the factors to develop therapies that may be safer, and more widely applicable than therapies with the cells themselves. However, MSCs modulate their anti-inflammatory effects in multiple ways that appear to be responsive to the different microenvironments created by different tissue injuries. Therefore, MSCs may be the therapy of choice for some diseases.

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