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Cellular Therapy for Sepsis: A New Hope?

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Konstantin Tsoyi and his colleagues have published an exciting work on the beneficial effects of carbon monoxide (CO) that improved efficacy of mesenchymal stromal cells (MSCs) (1). MSCs preconditioned with CO attenuated organ injury, increased bacterial clearance, promoted resolution of inflammation, and improved survival in mice with polymicrobial sepsis (1). Importantly, CO preconditioning preserved the efficacy of MSCs when they were administered at 6 hours post sepsis induction time. The salutary effects of these preconditioned cells were mediated by specialized proresolving lipid mediators (SPMs), particularly D-series resolvins.

Sepsis is a detrimental inflammatory response to infection. Despite its increasing incidence (10% annually) (2) and high mortality rate (highest in non-cardiac intensive care units) (3, 4), there is no FDA-approved drug available that specifically targets this fatal menace. The standard therapy for sepsis is symptomatic, and is becoming less effective due to the antibiotic resistance of microorganisms and potential side effects of vasopressors, such as norepinephrine.

Many successful preclinical basic science studies demonstrating efficacy of various pharmacological agents in animal models of sepsis have been translated to clinical trials. Unfortunately, none of them advanced to the clinical practice (5-8).

Recently, the cellular therapy is becoming an attractive candidate. Particularly, paracrine properties of mesenchymal stem cells (MSCs) have been shown to be important: interleukin-1 receptor antagonist, keratinocyte growth factor, interleukin-10, angiopoietin-1, prostaglandin E2, and antimicrobial factor LL-37 are the most commonly described paracrine soluble factors that have been shown to attenuate severity of acute lung injury (9). An exciting new trend is the modulation of MSCs to improve their survival, engraftment and paracrine abilities using different approaches (examples of MSCs modulation to enhance their paracrine activity are summarized in Table 1). Although the preconditioning of MSCs with hypoxia is commonly used by investigators (10, 11), Tsoyi et al. first reported

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beneficial effects of MSCs preconditioned with CO in a murine model of sepsis. While those inspiring new discoveries are celebrated, there are a few issues that the scientific community should focus on in the future. Those include:

1. Exploring precise mechanisms of how preconditioned MSCs work: the question whether the paracrine activity of MSCs, namely the release of various mediators is specific to preconditioning agent should be answered. For instance, the specialized pro-resolving mediators vary in the nature consisting from different proteins, peptides, gaseous mediators, and specialized lipid mediators i.e., lipoxins, resolvins, protectins, and maresins (12).

2. Identifying active constituent secreted by MSCs. Although Tsoyi and his colleagues demonstrated that the beneficial effects CO-preconditioned MSCs were mediated by 5- and 12/15-lypoxigenase pathway, specific role of resolvins remain incompletely understood (1). This is especially the case when the resolvin alone did not affect phagocytic ability of neutrophils (1). It is quite possible that MSCs paracrine response is none specific to CO or other stimuli.

3. Determining long-term effects of preconditioned MSCs. The question of how long the preconditioning effects last remains unanswered. Are there any side effects? Is it possible that consistent and overexpression of anti-inflammatory factors might paradoxically affect immune responses depending on the preconditioning agent and/or the pathological condition? A similar question can be asked about pro-inflammatory as well as procarciogenic effects of those preconditioned cells.

4. Clinical applicability is challenging. However, previous and the present study by Tsoyi et al. on the salutary effects of MSCs' secretome and their enhanced paracrine activity open future therapeutic options using cell-free therapies. For instance, metabolically stable analogs of promising specialized pro-resolving mediators, including different proteins, peptides and lipids can be isolated or newly synthetized and tested in clinically relevant large animal models that closely mimic human inflammation/infection for efficacy and safety in order to successfully translate to the clinical trials. The use of cell-free conditioned media should be considered as well. Finally, the animal model choice is critically important as most of previous successful preclinical studies that have been followed by failed clinical trials used rodent models.

Nevertheless, chemical or mechanical stimulation to enhance potency of MSCs clearly help these cells survive and be metabolically active longer time in harsh in vivo environment associated with severe inflammation. The work by Tsoyi and his colleagues shed a new light in this specific field, demonstrating efficacy of CO preconditioning that brought the cell-based therapy to the next level.

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Table 1

Examples of different methods of MSCs preconditioning/modulation

Preconditioning/Modulation	Type of study	Outcome	Reference
Preconditioning with hydrogen sulphate	Rat ischemic stroke model	Increased BDNF and VEGF and improved neurological function	Zhang Q et al. Oncotarget 2016 [ePub]
Preconditioning with trimetazidine	Rat myocardial I/R injury	Increased HIF-1a and improved survival	Hu X. J Clin Exp Med 2015; 8:16991–17005
Preconditioning with hypoxia	Mice myocardial infarction model	Increased leptin and improved post-myocardial infarction remodeling	Chen P et al. 2014; 9:e103587
miR-375 overexpression	Mice wound healing	Increased hepatic growth factor and reduced fibrosis	Sheng W et al. Am J Transl Res 2016; 8:2079
Physioxic (5%O_2) preconditioning	Rat spinal cord injury	Increased trophic and growth factors and improved axonal regeneration	Zhilai Z et al. Brain Research 2016; 1642:426–435
Preconditioning with TLR-3&4	Mice colitis model	Increased immunosuppressive factor IDO and decreased clinical signs of acute colitis	Fuenzalada P et al. Cytotherapy 2016; 18:630
Preconditioning with TNFa/IL-1b/Nitric oxide	Rat radiation –induced intestinal injury	upregulated IGF-1, bFGF and VEGF and improved survival and improved structural and functional restoration of intestinal injury	Chen H et al. Scientific Reports 2015; 5:8718
HO-1 overexpression	Diabetic rat	Increased VEGF and improved wound healing	Hou C et al. Biomaterials 2013; 34:112
Preconditioning with melatonin	Rat acute renal failure model	Overexpressed antioxidant enzyme catalase and superoxide dismutase-1, increased bFGF and HGF and improved renal function	Mias C et al. Stem Cells 2008; 26:1749