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Is A Part Better Than The Whole for Cell-Based Therapy?

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The acute respiratory distress syndrome (ARDS) is a devastating clinical condition common in patients with respiratory failure in the intensive care unit. It is associated with high mortality rates and long-term physical and psychological dysfunction among survivors[1, 2]. Based on promising preclinical data, clinical trials with mesenchymal stem or stromal cells (MSC) for ARDS are underway and constitute a new therapeutic approach[3]. Although no safety issues have been identified[3], there remain some concerns with giving large numbers of live MSCs intravenously, up to 10 million cells/kg per dose, in critically ill patients with systemic inflammation and pulmonary vascular dysfunction[4]. As a potential alternative approach, in the current issue of *Anesthesiology*, Varkouhi et al. tested the therapeutic use of extracellular vesicles released by human umbilical cord derived MSC in a well-established rat model of severe *Escherichia coli* (*E.coli*) bacterial pneumonia as an alternative to giving live cells, bypassing these biological concerns[5].

Once considered cellular debris or, more recently, as biomarkers of disease progression, extracellular vesicles (EV), comprised of exosomes, microvesicles and apoptotic bodies, released by endogenous living and dying cells are now recognized as important mediators of cellular communication and function[6]. EV are a heterogeneous group of anucleate vesicles with a diameter of 50 to 1000 nm that are released from intracellular compartments as exosomes or by budding off the plasma membrane as microvesicles in response to diverse physiological or pathophysiological stimulus. Through its cargo containing bioactive molecules such as proteins, mRNAs, microRNAs and organelles (i.e., mitochondria), and its interaction with target cells, EVs are recognized as having significant biological properties[7].

Multiple pre-clinical studies have demonstrated the therapeutic potential with MSC for acute lung injury in both small and large animal models despite limited engraftment rates of 1 ~ 5%. The therapeutic effects of MSCs appeared to arise in part from the secretion of growth factors such as keratinocyte growth factor, anti-inflammatory products such as PGE_2 or Lipoxin A4, anti-permeability factors such as angiopoietin-1, and antimicrobial products such as LL-37 or Lipocalin2[8]. Although the safety profile of MSCs in clinical trials has been excellent to date, some concerns still persist concerning their tumorigenic potential[9]. As an alternative to live cells, multiple investigators have reported beneficial effects of MSC derived conditioned medium or EVs for various organ injury models, including a recent study in an *ex vivo* perfused human lung preparation that was injured with live bacteria[10]. In the current study, similar to MSCs[11], Varkouhi et al.[5] found that the intravenous administration of MSC EVs or EVs released from MSC primed with interferon-γ (IFNγ) increased survival in adult male Sprague-Dawley rats injured with *E.coli* pneumonia at 48 h. Pretreatment with IFNγ was used to upregulate immune related genes in MSCs, including

major histocompatibility complex, co-stimulatory molecules such as CD80 or CD86, and indoleamine 2,3 dioxygenase to potentially increase the antimicrobial activity of the released EVs[12]. The use of interferon-γ was similar to the strategies used by other investigators to pretreat MSCs, such as with Poly (I:C)[13], carbon monoxide[14], or hypoxia[15], to enhance the therapeutic properties of the cells and the released EVs. Surprisingly, only IFNγ primed MSC EVs but not naïve MSC EVs reduced alveolar-arterial oxygen difference, lung protein permeability, and alveolar inflammation and enhanced endothelial nitric oxide production in the injured lung compared to controls. The lack of benefit of naïve MSC EVs may reflect a "survival bias" as suggested by the authors because one third of the control animals did not survive to 48 h, the time period where all the biological measurements were made in the surviving rats. However, both IFNγ primed and naïve MSC EVs increased *E.coli* bacteria phagocytosis and killing in human THP-1 derived macrophages *in vitro* which were consistent with the findings from previous investigations[16, 17].

There are some limitations to these studies which will require further research to more clearly define the potential therapeutic use of MSC EV in ARDS. (1) Although IFNγ primed MSC EVs increased macrophage phagocytosis of *E.coli* bacteria *in vitro* and numerically decreased the bacterial CFU levels in the injured alveolus *in vivo*, MSC EVs were administered only 30 minutes following initiation of injury. Experiments are needed with administration at later time points to determine whether the phenotype of IFNγ primed MSC EVs will have therapeutic value once the lung injury has been present for a longer period of time, similar to what would be the case in the clinical setting of ARDS. (2) In order to determine the mechanisms for the priming effect of IFNγ, additional studies are needed to assess the mRNA, microRNA and protein content of IFNγ primed MSC EVs compared to naïve EVs . (3) Prior to any clinical trial, any differential effects of MSC EVs based on sex need to be elucidated. (4) And, perhaps more importantly, priming MSC with IFNγ changed the size distribution of the released EVs, emphasizing the need to understand whether exosomes or microvesicles was driving the beneficial response.

Despite these limitations, the current study provides more evidence that EVs may be a viable alternative to using live MSC cells for treatment of ARDS. The benefits include ease of storage, avoiding dimethyl sulfoxide for preservation and the need for a bone marrow transplant facility, avoidance of using live cells that could be associated with as yet unknown safety issues, the potential to modify EVs with pretreatment of the MSCs to enhance the therapeutic effects, and the potential to administer higher and more frequent doses than may be possible with live MSCs. However, the major challenge for clinical translation of EV therapy is how to scale up the production of MSC EVs since the potency is approximately 10 times less than the MSCs themselves[16]. Given that a typical MSC dose is 10 million cells/kg or 700 million cells for a 70 kg patient[3], future clinical trials with MSC EVs may require isolating EVs released from up to 7 billion cells per patient, which may be logistically impossible. Studies are on-going to determine whether the source of the MSCs, whether from the umbilical cord, adipose tissue or bone marrow, or the method of priming, IFNγ, Poly (I:C)[13], carbon monoxide[14], and hypoxia[15], may reduce the number of MSCs that are required to generate enough EV for a therapeutic response.

Despite extensive research and numerous preclinical studies identifying various biological mediators, there are no specific pharmacological therapies for ARDS, and treatment is largely limited to supportive care and lung protective ventilation. The manuscript by Varkouhi et al.[5] further adds to the biological and clinical rationale to study MSC or MSC derived EVs as a promising new therapeutic approach for ARDS.

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