STEM CELLS TRANSLATIONAL MEDICINE®

LETTER TO THE EDITOR

Response to: Mesenchymal Stem Cells: Time to Change the Name!

With great pleasure, we read the recent Perspective by Arnold Caplan in which he urges that we change the name of mesenchymal stem cells (MSCs) to "medicinal signaling cells" [1]. While a name should not be considered an impediment to scientific progress, it is the underlying expectation of the clinical effect of these cells that may encumber the role of MSCs in the field of regenerative medicine. According to the Cambridge dictionary, a stem cell is defined as "a cell, especially one taken from a person or animal in a very early stage of development that can develop into any other type of cell." Because the main functionality of MSCs in vivo is not multipotency, but rather immunomodulatory and trophic, it is argued that we should not call them stem cells after all.

We must admit that, when our group started to work with bone-marrow derived MSCs, we called them mesenchymal stem cells because they were able to differentiate into bone, fat, and cartilage in vitro, or at least express the corresponding markers. In aiming at cartilage regeneration, we mixed chondrocytes and MSCs, with the initial hypothesis that the environment would stimulate MSC differentiation [2]. Different groups demonstrated similar results when mixing these cells and incorrectly concluded it was the MSCs that were responsible for the cartilage tissue regeneration [3]. Soon we came to realize that it was not the MSCs that created reproducible cartilage constructs. MSCs were found to induce chondrocytes and stimulate their chondrogenic capacity [4]. We found that preserving the pericellular matrix of chondrocytes (chondrons) enhanced this interaction with MSCs [2]. We also demonstrated that MSCs did not communicate solely through soluble factors, as direct cell–cell contact through gap junctions played an important role in the cellular crosstalk [4]. We and others showed that MSCs disappeared from cocultures while stimulating tissue regeneration [3, 5].

In his Perspective, Arnold Caplan neatly describes the evolving insight that MSCs are derived from pericytes. Pericytes have been traced in vivo in different tissues and found to retain their original identity [6, 7]. It remains unclear, however, how long and exactly through what mechanisms these pericytes stimulate a host response. For example, while trophic factors excreted by MSCs seem to inhibit scar formation and apoptosis, the role of extracellular vesicle excretion and their amelioration of inflammation is only just recently being explored [8]. Although there is evidence that MSCs can remain traceable after several weeks in vivo, it is unclear how implanted cells behave in the human being [9].

Based on our clinical work and supported by the signaling cell hypothesis, we assessed the presence of donor DNA from allogeneic MSCs 12 months after implantation in cartilage defects in the knee [10]. In this first-in-human trial, allogeneic MSCs were mixed with autologous recycled chondrons and implanted within a single surgery. DNA analysis using short tandem repeats confirmed our hypothesis that MSCs would disappear over time. Indeed, the fact that no donor MSC DNA could be traced after 12 months supported the hypothesis that the MSC-induced host response was responsible for the new tissue formation, not (stem) cell differentiation. Although to date many clinical trials have been performed with both allogeneic and autologous MSCs, to our knowledge, no other clinical trials have demonstrated the fate of these cells. Thus, there is sufficient evidence to stop calling MSCs stem cells. As long as we explain to our patients what the realistic and desired effect of these pericytes is, a name is but a name.

It is more important to stress that many questions remain to be answered. For example, when MSCs are injected into the human being, which trophic factors and vesicles are these cells excreting, why, and for how long? What is the influence of the microenvironment, (joint) homeostasis, and cell–cell interactions on these bioactive factors and subsequent tissue regeneration in humans? Do pericytes and MSCs derived from different tissues have the same immunological and biological clinical effect? In turn, what response, if any, does the immune system have on pericytes and MSCs? And more importantly, how can we steer these signaling cells to give the correct signals to the host within a desired time frame? It is the answers to these and similar questions that will improve our understanding and applicability of these important cells. In the meantime, we will call MSCs medicinal signaling cells, not mesenchymal stem cells.

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DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

The authors indicated no potential conflicts of interest.

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