# Hints to improve the success rate of cellular therapy based on mesenchymal stromal cells (MSCs): secretome of senescent MSCs has a negative paracrine effect on healthy cells by reducing the stemness and promoting the senescence

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Cell senescence has been regarded as a strictly intracellular response, with the entire signaling circuitry, which takes place within the cell. Recent findings have demonstrated that several secreted molecules are associated with, and contribute to senescence proliferative arrest.
It is evident that senescence process may greatly affect also the composition of mesenchymal stem cells (MSC) secretome through a shift from a functional paracrine signaling to production of senescent-associated secreted factors that have potent autocrine and paracrine activities. Changes in secretome profiles of MSC may great impair their activities, which depends on the capability to secrete many factors, like cytokines and chemokines.
We performed a comparative analysis of human MSC secretome from young and replicative senescent cultures and evaluate if factors secreted from old MSC cultures may induce senescence, or arrest proliferation, or promote cytotoxic effects in young cells.
Our data strongly evidenced that senescence-associated secretory phenotype (SASP) implements a full senescence response in young cells suggesting that a few senescent cells in the MSC stem cell pool may be a potent trigger for ageing phenomena through a paracrine signaling cascade.
We demonstrated that secretion of IGFBP4 and IGBP7 has a significant senescent paracrine effect on young MSC. Moreover, the inhibition of these factors also reduced the percentage of apoptosis and promoted cell growth suggesting that may have a pleiotropic effect on MSC biology.
In conclusion, we could speculate that our study could pave the way to further investigations aiming to modify, in the near future, the current in vitro MSC expansion protocols for therapeutic purposes to avoid or reduce the occurrence of negative senescence related effects.