Title: **Phenotypic Changes observed on tissue specific EC during activation, and on aMSC after the co-culture of it with the activated EC**

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Abstract:

After any injury damage any organ, there are a common pattern of sequence of events to promote tissue's repair but if this process is insufficient it led to scar formation and/or its fibrosis. The steps of this process may be summarized as follow

After an Injury happens, damaged Tissue produces chemotaxis substances to mainly attract polymorphonuclear cells (PMN) to the area. Monocyte continuing cleaning the area, and producing chemotactic signals that attract local and distance Stem cells as well as elicit an organ specific lymphocyte (EC) activation. EC and Stem cells start the stroma and parenchymal repair, but if the process is exceeded for the properties of the wound the same process led to the development of tissue fibrosis and/or scar formation.

Based on this classic sequence of event chain, modern knowledge allows as to distinguish 3 different faces of the inflammatory reaction: acute phase, sub-acute phase and chronic phase. The first is Antimicrobial and pro-oxidative and only last 48 hours. The second is the one where the regeneration process start and end. Happens during the day 2 until day 12 to 17, according the considered tissue. The third phase is profibrotic and anti-regenerative.

Based on the above-mentioned concepts we have developed an immune modulatory treatment to direct and support the action of different kinds of stem cells during the repair process utilized for chronic conditions. Different immunohistochemistry and molecular biology studies support our assumption that Effector Cells became the main responsible and directors of the repair process and their inclusion into different repair process is very important to overcome the limitations of the cell therapy.

The phenomena that summarize the rational of our protocol may be synthetized in the following next 4 points:

- In vitro MNC activations, when challenged with a CNS antigen (Cerebrolysin), induce Effector Cells (EC) against differentiated CNS cells

- However, these effector cells also produce different epigenetic factors (v.g Neurotropins) that induce Stem Cell to differentiate into neurogenic (neuroblast like) cells.
- EC are attracted to be in touch with stem cells. It is a chemoattraction and a receptor mediated intercellular phenomenon that develops gap junctions in between both cells and different interexchange of paracrine factors.
- As a result of this physical and paracrine crosstalk, Stem cells became neural progenitor cells and EC became Treg cells

The model have been also tested into some other different chronic conditions in between them we also have obtained very good result recovering fibro adipose atrophied skeletal muscles and advanced osteoarthritis. In both case fibrotic process was reversed and stroma and parenchymal tissues were regenerated.

The presentation summarize the phenotypic changes occurred on EC and MSC during the tissue regeneration process and some animal experiments that support these changes as well as the nececity of the immune system to lead these process.