Extracellular vesicles with improved therapeutic capacity

DESCRIPTION OF THE TECHNOLOGY

Chronic inflammation is a pathophysiological state caused by the uncontrolled activation of the immune system A wide variety of diseases cause chronic inflammation, such as graft-versus-host disease, acute rejection of a transplanted organ or autoimmune pathologies.

Mesenchymal stromal cells and the released extracellular vesicles (EVs) have demonstrated immunomodulatory capacity in preclinical setting, but when this therapies were transferred to clinical arena the results were inconclusive. In this technology, the IIS La Fe team has genetically modified wild type MSC and generated extracellular vesicles (EVs) with greater therapeutic potency than those releases by wild type MSCs.

The invention presents the generation of a new line of stromal mesenchymal cells that overexpress HIF-1α and hTERT through genetic modification, which is cultured in the presence of secreted TNF-α, IFN-γ and IL-1β for 48 hours (EVs) with a greater therapeutic potential than those secreted by unenhanced mesenchymal stem cells (MSCs).

These new EVs exert a greater therapeutic effect and in turn allow unlimited cell growth to obtain a stable and homogeneous source of vesicles with improved therapeutic functions. By overexpression of HIF-1α, therapeutic improvement is obtained, while overexpression of hTERT generates unlimited and constant cell division. The main advantage of the invention is the combination in the use of genetic modifications with the specific culture protocol.

MARKET APPLICATION SECTORS

The main sector interested in this invention is composed by the pharmaceutical companies that are currently working on the development of therapies based on stromal mesenchymal cells or extracellular vesicles.

TECHNICAL ADVANTAGES AND BUSINESS BENEFITS

• Overexpression of HIF-1α by genetic modification of MSCs using lentiviral technology, which provides a greater immunosuppressive capacity (both in vitro and in vivo) to the vesicles secreted by pulp-derived stromal mesenchymal cells.

• Overexpression of hTERT through genetic modification of MSCs using lentiviral technology, which means that stromal mesenchymal cells do not enter replicative senescence, so that it is possible to use a few cell lines to obtain therapeutic vesicles without the line being depleted and it is necessary a test of different donors every little time.

• Stimulation of genetically modified cells with pro-inflammatory cytokines in order to activate their immunoregulatory capacity. This in turn induces a secretion of EVs with greater immunoregulatory capacity.

CURRENT STATE OF DEVELOPMENT

The results have been validated in murine models of ischemia, ulcerative colitis and delayed hypersensitivity with satisfactory results. Work is being done on scaling up the production of these EVs under GLP / GMP conditions and on regulatory documentation to be able to use this biological product in a *First in man* clinical trial.

INTELLECTUAL PROPERTY RIGHTS

National Patent EP20383170, dated December 29, 2020

Title: Extracellular vesicles derived from mesenchymal stromal cells genetically modified to overexpress hif-1a and htert.

COLABORATION SOUGHT

The inventors are looking for investors and companies interested in licensing the technology, as well as

strategic partners and new sources of funding to advance development.

RELATED IMAGES

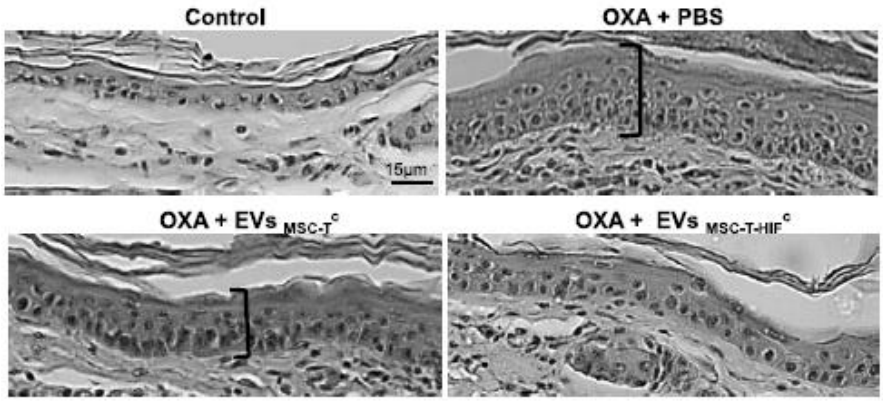

Figure 1. Representative images of the reduction of inflammation induced by activated MSC-HIF-TERT EVs in a delayed hypersensitivity murine model. The thickness of the mouse near dermis is indicated under normal conditions (control) and after treatment with Oxalozone followed by injection of physiological saline solution (OXA + PBS), activated MSC-TERT EVs (OXA + EVsMSC-Tc) o Activated MSC-TERT-HIF EVs (OXA + EVsMSC-T-HIFc).

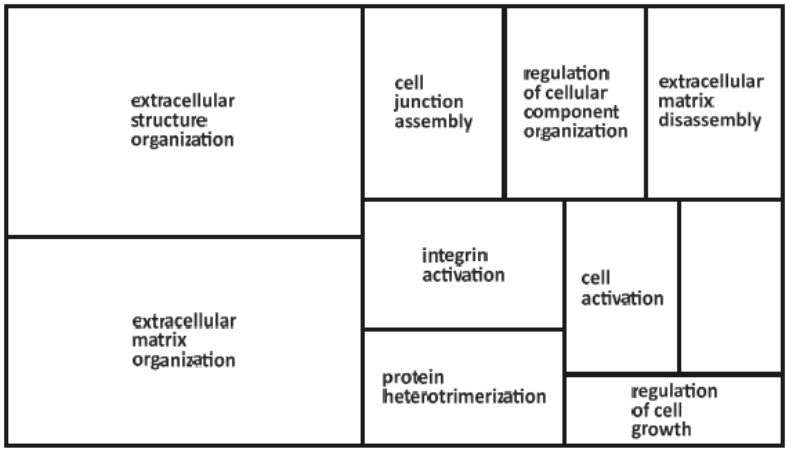

Figure 2. Bioinformatic analysis of biological processes differentially expressed in activated MSC-HIF-TERT EVs compared to wild type EVs. The most representative biological processes are shown in boxes. The area of each box corresponds to the specific weight of each process,

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