Category :**Sepsis/septic shock: management**

A53 - ***A novel virotherapy encoding human interleukin 7 enhances ex vivo lymphocyte functions in immunosuppressed septic shock and critically ill covid-19 patients***

M Crausaz [1] ; G Monneret [2] ; P Martin [1] ; F Conti [2] ; A LUKASZEWICZ [3] ; G Inchauspé [1] ; F Venet [4]

[1]Transgene, Department of Infectious Diseases, Lyon, France, [2]EA 7426 Pathophysiology of injury-induced immunosuppression (PI3), Lyon 1 University/ Hospices Civils de Lyon / bioMérieux, Hôpital Edouard Herriot, Lyon, France, [3]Hospices Civils de Lyon, Hôpital Edouard Herriot, Service d´anesthésie-réanimation, Lyon, France, [4]Hospices Civils de Lyon, Hôpital Edouard Herriot, Laboratoire d'Immunologie, Lyon, France

Introduction:

After viral or bacterial sepsis, most intensive care unit (ICU) patients enter a state of profound immunosuppression contributing to patients' worsening. Transgene has developed an immunotherapy based on a viral vector encoding human interleukin-7 (hIL-7) to restore both innate and adaptive immune responses. Here, we assessed the capacity of hIL-7 to improve *ex vivo* T lymphocyte function from septic shock and COVID-19 patients.

Methods:

Primary human hepatocytes were transduced with MVA-hIL-7-Fc, a recombinant Modified Vaccinia virus Ankara (MVA) encoding the hIL-7 fused to the human IgG2 Fc fragment, or with empty MVA as control. Cell culture supernatants were harvested for further assays. T cells were collected from ICU patients (septic shock = 11, COVID-19 = 29) and healthy donors (n = 21). STAT5 phosphorylation, cytokine production (ELISpot and intracellular staining) and cell proliferation were assessed upon TCR stimulation with supernatants containing or not hIL-7 produced after MVA transduction or with the counterpart recombinant hIL-7 (rhIL-7).

Results:

Patients with viral and bacterial sepsis display T lymphocyte alterations compared to healthy donors with a decreased production of cytokines and a decreased proliferation capacity. Supernatant containing hIL-7 induces STAT5 phosphorylation in CD3 lymphocytes of all patients. With 90% of responders, hIL-7 boosts cytokines production (single and double IFN-TNF) and T lymphocytes proliferation capacity at the same level as rhIL-7 in both cohorts whereas empty MVA has no effect.

Conclusion:

This study indicates that hIL-7-Fc produced after MVA transduction initiates IL-7 signaling through the phosphorylation of STAT5 and restores *ex vivo* human lymphocyte functions in cells from septic patients with acquired immunosuppression. This proof-of-concept study, along with experimental results in animal models, supports the clinical development of the MVA-hIL-7-Fc in sepsis immunosuppressed patients.