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Reversing lymphocyte anergy in septic syndromes: an innovative therapeutic strategy for prevention of mortality and secondary nosocomial infections

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Despite marked improvement in critical care medicine and almost 20 years of anti-inflammatory clinical trials, septic syndromes (association of an infection and a systemic inflammatory response syndrome) represent a major health care problem worldwide. During the last 20 years, septic mortality has remained constant (up to 60% in septic shock) and its incidence has been continuously rising, due to the constant aging of the population and the better care of co-morbidities (diabetes, cancer …). Sepsis is currently the first cause of death in intensive care units. Most importantly, it is projected to represent one million cases per year before the year 2020 in the USA alone.
The dramatic immune alterations in severe septic syndromes are schematically described as a biphasic process with the occurrence of both pro and anti-inflammatory mechanisms alternatively predominating overtime. After a short initial pro-inflammatory response (responsible for the phase of shock and multiple organ failure), a state of immunodepression is rapidly occurring induced by anti-inflammatory / regulatory mechanisms acting as a negative feedback. The intensity and duration of this phase of immunosuppression appear to be closely correlated with mortality and the development of nosocomial infections in septic patients. There is thus a justification for immunostimulatory therapies in sepsis. Initial clinical trials testing IFN-γ or GM-CSF have shown promising results in monocyte functions restoration. However, so far, no therapeutic strategy targeting the adaptive / lymphocytic part of the immune response has been tested in sepsis.
Sepsis-induced lymphocyte dysfunctions include a massive increase of the percentage of regulatory T cells, induction of apoptosis, decreased proliferative response (to recall antigens) and decreased expression of co-activating molecules (CD3, CD28) with concomitant increase in inhibiting co-receptor expression (PD-1, CTLA4). These alterations concur to the development of a state of lymphocyte anergy that likely participates in mortality, the development of secondary nosocomial infections and reactivation of dormant viruses in patients. In that sense, lympho-stimulating therapies may also represent good candidates for the treatment of severe sepsis. However, a beforehand necessary step to their use in patients is to test their capacity to reverse sepsis-induced dysfunctions. The goal of this study is thus to better understand the mechanism(s) leading to sepsis-induced lymphocyte alterations and to investigate the therapeutic effect of specific lympho-stimulating treatments on these alterations.
The research program will be in three parts:

- Clinical study in patients

In the context of a clinical research protocol ongoing for several years in the Hospices Civils de Lyon, 30 patients will be closely monitored for markers of lymphocyte dysfunctions. Lymphocyte anergy (decreased proliferation in response to mitogenic or recall antigen stimulation) will be investigated in parallel with potential mechanisms: 1/ Decreased TCR and co-stimulatory receptor expression 2/ Increased inhibitory co-receptor expression 3/ Inhibition by regulatory T cells 4/ Increased apoptosis.

- Ex vivo pharmacological study

In a subgroup of patients, we will study the capacity of specific treatments to act on the beforehand listed mechanisms of anergy and to restore of normal lymphocyte functions

after sepsis. Peripheral blood mononuclear cells will be purified from septic patients and incubated ex vivo with the molecules.

- In vivo pharmacological study

We will develop a clinically relevant model of sepsis recapitulating the observations made in patients. In this murine model, the mechanisms identified in patients as potentially responsible for the development of lymphocyte anergy will be precisely investigated and the therapeutic effect of specific treatment administration on the development of these immune alterations, on the occurrence of secondary organ dysfunctions, on mortality after the induction of sepsis and the response to a secondary infectious challenge will be studied.

If this project is successful, the preliminary studies to the administration of lympho-stimulatory drugs in septic patients will be performed. Beyond septic syndromes, this approach may also represent an innovative therapeutic strategy for the prevention of the development of secondary nosocomial infections in severely injured ICU patients (burns, trauma, pancreatitis, surgery) who present similar mechanisms of induced immunosuppression.