Stem Cell Therapy for Critical Illness involving Sepsis and Organ Injury

Professor Claudia dos Santos

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Professor Claudia dos Santos is interested in studying the disease processes and the therapeutic targets related to critical illnesses involving sepsis and organ injury. Here we discuss the research background of professor dos Santos and her work on stem cell therapy in animal models of sepsis and lung injury.

Your research is focused on studying the critical illness caused by sepsis and organ injury. So to start, can you describe to the readers the nature of these conditions and their potential impacts on health and survival?

Sepsis is a life-threatening condition that occurs when the body has an overwhelming immune response to infection. Severe sepsis patients are often admitted to the intensive care unit, where they receive life supportive care. Most people who die following sepsis or a sepsis-like disorder call systemic inflammatory response syndrome (SIRS) die from Multiple Organ Dysfunction Syndrome (MODS), which accounts for up to 80% of all deaths in modern ICUs. Any organ can be a target of MODS including the lungs, the kidneys, the brain, the liver, the gut or the blood coagulation system. Although advances in care, diagnosis and management of infection have reduced early mortality, no specific treatments have been identified to treat MODS. Moreover, survivors experience significant disability after discharge from ICU, and mortality risk are increased for survivors long term.

How did your interest in studying critical illnesses begin and what has been the motivation behind it?

During my medical school training, I noticed that I gravitated towards the sickest patients. I was particularly drawn to the challenge of diagnosing and managing life-threatening conditions requiring sophisticated organ support and invasive monitoring. Many critically ill patients are in extremis, and their biology is complex and requires extensive knowledge of medicine to understand how multiple crucial variables such as past medical history, medication, psychosocial and economic factors can contribute to the clinical outcome and the success of the treatment. I was especially drawn to being on the cutting edge of research and technology, and I found that I enjoyed the technical aspect of a procedure-intensive subspecialty. I also liked working with critical care nurses, doctors and other adjunct medical professionals in intensive care units. These are a wonderful group of dedicated and hard working professionals who shared with me a strong sense of purpose.

In the course of your research, you have studied the application of stem cells in the treatment of sepsis and associated tissue injury. Can you explain what stem cells are and why are they of therapeutic value in these cases?

Stem cells are undifferentiated biological cells that retain the potential to differentiate into specialized organ cells (e.g. muscle, liver or lung cells). This particular feature has raised the interest in stem cells as a therapeutic tool for tissue regeneration and repair. Stem cells also possess other biological characteristics such as the ability to release molecules with the potential to regulate the function of the immune system. The research done at my laboratory has shown that bone marrow-derived mesenchymal stem cells ameliorated the inflammatory and injurious immune responses in animal models of sepsis and acute lung injury. These therapeutic effects are believed to be mediated by the release of anti-inflammatory molecules rather than by the tissue regeneration properties of stem cells. In addition, recent findings from my group suggest the ability of stem cells to reprogram the immune cells to produce less inflammatory mediators, and to enhance the clearance of the bacteria causing the inflammation.

Are you planning to extend your research on stem cell therapy further? What might be the scope of the next step?

Yes. The major goal of my research is to translate our current knowledge of stem cell biology to the development of novel therapeutic strategies for the treatment of sepsis in critically ill patients. To this end, we have established collaborations with the Canadian Critical Care Trials and Translational Biology Groups. Both groups are involved in the first human trial of stem cells for the treatment of severe sepsis. Our role will be to profile genetic material from septic patients who received stem cells and compare it to patients who received placebo to determine how patients respond to treatment and determine the markers that can predict response to therapy as well as other important clinical outcomes such as surival. We are also working on improving stem cell technologies by optimizing and enhancing the anti-inflammatory and anti-bacterial potential of cells. In the future, we hope cell-free approaches may also become available for the treatment of sepsis, acute lung injury and multi-organ failure.

Promise and Challenges of Stem Cell Therapy in Sepsis and Organ Injury

Professor dos Santos and her group have recently validated the therapeutic potential of stem cells in controlling the complex inflammatory and immune responses associated with sepsis and sepsis-induced organ injury in clinically relevant animal models.

A STORY OF CRITICAL ILLNESS AND ORGAN DYSFUNCTION

Severe sepsis is a leading cause of morbidity and mortality worldwide. It is the most common reason for admission to the intensive care unit (ICU) accounting for 20% of such admissions. Although early identification, aggressive resuscitation, administration of antibiotics and supportive care has reduced mortality, this remains unacceptably high. From a health care perspective the aggregate healthcare cost reaches $20.3 billion per year, sepsis represented 5.2% of the national costs for all hospitalizations in 2011 in the US. Moreover, post-acute care of survivors is estimated to be as high as $3.5 million per individual at 1 year post-ICU discharge.

The vast majority of ICU deaths occurring among critically ill septic patients are caused by Multiple Organ Dysfunction Syndrome (MODS). The latter is a complex condition in which the normal physiological function of the affected organ cannot be maintained without intervention. It usually involves two or more organs, including vital organs such as the lungs (acute respiratory distress syndrome), the kidneys (acute kidney injury), the brain (septic encephalopathy), the liver (acute liver failure), the gut or the blood coagulation system. The degree and severity of organ failure is profoundly dependent upon the patients' age and pre-morbid condition, with older and frailer patient doing worst despite the use of proper medication and life support.

Sepsis and organ dysfunction involve a series of abnormal reactions of the cellular and soluble components of the innate immune system, the biological system responsible for coordinating our response to injury and infection. In progressive cases, and for yet unclear reasons, over- or under-activation of the innate immune system combined with microcirculatory failure results in MODS. This intricate pathogenesis represents a challenge for identifying effective treatments against sepsis and MODS. Targeting a single pathway is unlikely to be effective in modulating the complex inflammatory and immune responses. Indeed, numerous specific pharmacological agents have failed to produce significant benefits in clinical trials of severe sepsis.

STEM CELLS: ORIGIN AND BIOLOGICAL CHARACTERISTICS

Stem cells are undifferentiated cells that retain the potential to differentiate into a variety of cell types with different functions (a feature referred to as pluripotency). They are found in multicellular organisms, but are most commonly isolated from mammals. There are two broad types of mammalian stem cells: embryonic stem cells, which are isolated from embryos at early developmental stages, and adult stem cells, which are found in various adult tissues. In terms of clinical application, stem cell may be derived for either allogeneic use (from a donor to a patient) or for autologous use (from the patient's own body). Autologous cells, however, require significant preparation time (weeks) and they would not be adequate for use in critically ill patients who will likely need the cell therapy immediately after admission to the ICU. 'Therefore a bank of stem cells collected from healthy donors will have to be made available for clinical use' says Professor dos Santos.

Mesenchymal stem cell therapy reduced the complex inflammatory reactions underlying sepsis in a clinically relevant mouse model, and reconstituted the components of the immune system to enhance the clearance of the causative microbes

STEM CELL THERAPY FOR SEPSIS AND ORGAN INJURY

Among the various subtypes of adult stem cells, bone marrow-derived stem cells, which are commonly known as Mesenchymal Stem/Stromal Cells (MSC), have gained increasing interest for the treatment of diseases involving inflammation and organ injury. The research done by Professor dos Santos and her group has shown the ability of MSC to ameliorate the inflammatory responses associated with acute lung injury and sepsis in mouse models, indicating their therapeutic potential. Importantly, these therapeutic effects were achieved after the onset of experimental sepsis/organ injury, mimicking the natural disease and

a clinically relevant therapeutic approach.

Regarding the mechanisms underlying the therapeutic effects of MSC in models of sepsis-induced MODS, it is uncertain whether the pluripotent nature of these cells plays the most significant role. 'Frankly, pluripotent mechanisms involving stem cell differentiation are not thought to underlie the beneficial effect conferred by MSC in sepsis', says Professor dos Santos. In contrast, other characteristics of stem cells, particularly their ability to release anti-inflammatory mediator molecules, have been proposed as effectors of the MSC-conferred protection from injury. Moreover, recent findings by Professor dos Santos and her team have postulated a role of MSC in 'reprogramming' the inflammatory response in sepsis, indicating that the beneficial effects of MSC extend beyond the suppression of inflammation. These combined immunoregulatory and immunomodulatory effects suggest MSC therapy has the pivotal advantage of addressing the complexity of immune abnormalities observed in sepsis and MODS, and may represent a promising novel treatment strategy affecting the inflammatory response at multiple levels.

In addition, the work of Professor dos Santos has also shown that MSC could reconstitute the physiologic status of the immune system, allowing the immune cells to fight and clear the bacteria causing the sepsis. This effect adds an extra level to the therapeutic potentials of MSC in sepsis, addressing the removal of the definitive cause of the disease.

CHALLENGES FOR THE MSC-BASED THERAPY

Despite the promising therapeutic effects of MSC in treatment of sepsis and organ injury, various important issues remain to be resolved before the full benefits of the technology are realised. 'The need to address these barriers to clinical translation is underlined by the limited clinical experience with MSC in critically ill patients to date', says Professor dos Santos.

The optimal route of administration of MSC is not known, with evidence supporting the intravenous, intratracheal and intraperitoneal administration routes. The optimal dosage regimen for MSC, including the lower effective doses, is also not clearly determined. Preclinical studies to date have used relatively poorly defined, heterogeneous MSC. Recently, more specific MSC subpopulations were identified, however, their capacity in attenuating organ injury remains to be determined. A standardized protocol for isolation and characterization of MSC versus other stem cell subpopulations is currently lacking, a consensus on minimal criteria for product development needs to be standardized for its use in sepsis patients. Furthermore, there is no validated method of measuring MSC bioactivity in the host after administration. Despite advances in MSC research, our understanding of the mechanisms of action remain incomplete. Of great concern is the tolerance of the immune system of the recipient to autologous MSC administration. MSC have long been believed to be hypoimmunogenic or 'immune privileged'—meaning that they do not provoke the innate immune system to elicit defence responses against them. This property will make it possible for stem-cells grown in culture, if proven safe, to be transfused similarly to how we transfuse other blood products today. It is not known whether rejection responses might influence the efficacy of allogeneic MSC therapies, and no definitive clinical advantage of autologous MSC over allogeneic counterparts has been demonstrated. In fact, MSC may exert therapeutic functions through a brief 'hit and run' mechanism. Notwithstanding, because this treatment will require cell delivery the remote risk of tumorgenicity exists, although no studies have shown any risk of malignancy.

CURRENT STATUS AND FUTURE PERSPECTIVES OF MSC THERAPY

Despite our incomplete understanding of MSC biology after delivery, their promising therapeutic effects in animal models of sepsis and organ injury have encouraged Professor dos Santos and other scientists to conduct initial clinical trials on human patients. The laboratory of Professor dos Santos is currently collaborating in an undergoing clinical trial with Dr. Lauralyn McIntyre and Dr. Duncan Stewart at Ottawa Hospital Research Institute in Canada to evaluate the safety and efficacy of MSC therapy in septic shock patients. The role of Professor dos Santos and her group is to profile genetic material from septic patients to identify biological markers of patient classification, disease prognosis and therapeutic effects. This work can potentially contribute to filling a part of the gap in the current knowledge of the functional and the therapeutic biology of MCS.

Researcher Profile

Professor Claudia dos Santos M.D. M.Sc. F.R.C.P.C.
Associate Professor of Medicine, Interdepartmental Division of Critical Care, Scientist, Keenan Research Centre for Biomedical Science of the Li Ka Shing Knowledge Institute of St. Michael's Hospital
Scientist, Institute of Medical Sciences, Collaborative Program in Genome Biology and Bioinformatics and Laboratory Medicine and Pathobiology, School of Graduate Studies, University of Toronto

Professor dos Santos is an associate professor of Medicine at the University of Toronto and a scientist at the Keenan Research Centre for Biomedical Science and the Li Ka Shing Knowledge Institute of St. Michael's Hospital. Her major interest is in the pathogenesis of sepsis, acute lung injury and multiorgan dysfunction syndrome. Her laboratory employs integrated systems biology and functional genomics approaches to: (a) understand host-dependent molecular mechanisms of acute organ failure, and (b) develop an "informed" approach to the discovery of novel molecular targets for therapy of sepsis and acute lung injury. Professor dos Santos has developed various model systems from basic epithelial cell stretch models to animal models of critical illness. Her group exploits whole genome approaches, such as microarray technology in vitro and in vivo, to identify novel molecular targets for therapy.

CONTACT

E: DossantosC@smh.ca
T: +1 416 864 8575
W: http://www.stmichaelshospital.com/research/profile.php?id=dossantos&

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