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EVENT ABSTRACT

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TISSUE REPAIR AND REGENERATION IN SPACE AND ON EARTH

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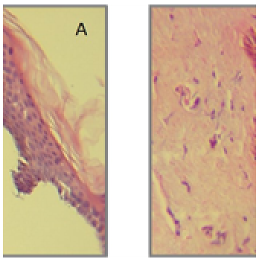
Repair/regeneration is the process that makes organisms resilient to injuries (trauma, burns, accidental wounds, surgery), allowing survival, restoration of the protective barrier and organism integrity.
Remarkable progress has been achieved in understanding the cellular and molecular mechanisms of tissue repair, but many of them still remain elusive and many questions are unanswered. For example, it remains unexplained why mammals have a tendency for imperfect healing and scarring, rather than full regeneration. Also the causes of failure in tissue repair mechanisms are poorly understood and currently the available therapies are limited [Eming et al., 2014].
It is known that wound healing is a complex set of processes, involving a number of cell lineages. Alterations in one or more of these events, that overlap and intertwine, result in defective repair, ranging from delayed healing and chronic ulcers to scarring and fibrosis. The different steps of tissue repair are regulated by a multitude of biochemical and physical factors, including gravitational/mechanical forces acting at cellular and tissue level. Moreover, several factors related to the state of patients and operative modalities are important for tissue repair and its complications: age, gender, overweight, systemic diseases (e.g. diabetes), wound contamination, non-physiological environment, urgency, emergency care, wound care, suturing materials and techniques.
On Earth, traumatic injury is a major cause of mortality and disability. In addition, millions of surgical wounds are performed annually in the course of routine surgery and medical care. Therefore, defective or delayed wound healing, chronic ulcers and fibrosis are important health and socio-economic problems [Sen et al., 2009]. They are caused by alterations mechanisms underlying repair, such as dysregulated immune function, chronic inflammation, impaired fibroblast function, defective ECM deposition, altered endothelial function, dysregulated apoptosis, etc...
Until now wound healing has not been considered as a major health problem in space because, during the current space missions, the occurrence of injuries, traumatic events and surgical emergencies has been considered unlikely. Despite the current considerations, future space exploration programs require long duration missions beyond LEO and hence health emergencies on board cannot be excluded, while medical evacuation times to Earth might become too long and the communication lag would render useless to guide the crew actions remotely. Therefore, medical care planning for future exploration missions should consider emergency surgery and trauma care, and meanwhile studies on repair processes in space are of paramount importance as wound healing is critical to survive trauma or surgery. Results of our previous studies, in agreement with those of other authors, showed microgravity-induced changes in mechanisms underlying tissue repair [Monici et al., 2011; Cialdai et al., 2017]. Experiments performed in real and simulated microgravity revealed alterations in fibroblast and endothelial cell function, changes in ECM production and dysregulation in apoptosis. Interestingly, in astronauts, deficient immune function, signs of chronic inflammation and insulin-resistance have been observed. These alterations, resembling some features of systemic diseases which impair wound healing on Earth, could affect the body's response to injury and could represent a model to study defective healing mechanisms [Demontis et al., 2017].
The experiment "Wound Healing and Sutures in Unloading Conditions", selected by ESA (ILSRA-2014-0043), aims to study the behavior of "in vitro" sutured wound models in weightlessness (ISS). The findings are expected to increase the knowledge on wound healing in weightlessness, suggest new pathways for tissue engineering, give cues for strategies promoting tissue repair/regeneration and improving the management of defective healing in space and on Earth.
The on-ground activities carried out in preparation of the experiment can be summarized as follows:
1) standardization of procedures for biopsy collection, model preparation, techniques for model culture and postflight analysis; 2) improvement of culture techniques to ensure tissue survival throughout the experiment; 3) analysis of tissue mechanical properties and development of a device to model physiological tensile strength in the tissue and measure its changes due to suture behavior and the healing process.
The sutured wound models developed for the experiment are based on skin and vein vessel biopsies cultured on dedicated hardware, in conditions that ensure their survival for over 3 weeks and allow to stretch the tissue, mimicking the physiological tensional strength, and monitor tension changes due to suture application and repair process at the wound site. Hence, not only histological and biochemical aspects, but also the biomechanical properties of sutured wounds can be analyzed.
For the in-flight experiment, after collection biopsies are maintained in modified, RPMI-based, organ culture medium at 4°C for storage and travelling to the launch site. Here, linear wounds are performed on skin by a scalpel and then sutured. The vessels are completely divided to perform an end-to-end vascular anastomosis. RPMI-based medium is replaced with modified, DMEM-based, organ culture medium. On the ISS the sutured wound models will be placed at 32°C for activation of repair mechanisms and then frozen at different time-points. During the experiment, the tensile strength in tissues will be monitored and morphological imaging of the sutured wounds is performed. In order to obtain information on the activation of tissue repair mechanism in weightlessness, post-

mechanism activation, fibroblast behavior, stiffness and strength in sutured tissues.
Beyond the development of the sutured wound models, their survival for a sufficient amount of time (at least 3 weeks) has been identified as a crucial point for the success of the experiment. Focusing on this problem, we developed a tissue culture technique based on tissue stretching and modification of organ culture media by adding proangiogenic substances and peptides. In addition to defining the requirements for the in-flight experiment, the on-ground activity has produced a significant result: this technique, which allows the survival of the tissue biopsies for over 3 weeks (Fig 1), can be applied also on ground in tissue culture and engineering for transplantation and regeneration, studies on tissue mechanical properties, studies for improvement of surgical techniques and materials.

FIGURE LEGEND:
Fig 1 – Skin samples cultured for over 3 weeks in common culture conditions (A) and using the culture technique developed for the in-flight experiment (B), which allows a better survival and preservation of the tissue.

Figure 1



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