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EFFECTS OF UNLOADING CONDITION ON WOUND HEALING PROCESS: EXPERIMENTS WITH HIRUDO MEDICINALIS

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Wound healing is a fundamental process for survival. It makes an organism able to repair a damage and restore physiological condition. The whole process involves the coordinated interaction of many different cell populations and biochemical molecules, such as proteins, proteases, growth factors, and extracellular matrix (ECM) components. Wound healing consist of four precisely programmed phases that follow one another and partly overlap. The events of each phase must happen in a definite and regulated manner. Hemostasis is the first phase and begins immediately after wounding. It is characterized by vascular constriction and fibrin clot formation. The clot and surrounding wound tissue release pro-inflammatory cytokines and growth factors, such as transforming growth factor (TGF)-β, platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and epidermal growth factor (EGF). Once bleeding is controlled, immune cells migrate into the wound (chemotaxis) and promote the inflammatory phase, which is characterized by the sequential infiltration of neutrophils, macrophages, and lymphocytes. During this phase bacteria and cell debris are removed from the wound and soluble factors are released. They induce cell migration and also stimulate cell division in the next phase.
The proliferative phase is characterized by angiogenesis, collagen deposition, granulation tissue formation, epithelialization and wound contraction.
In the last phase, the remodeling phase, collagen is reorganized and realigned along tension lines while apoptosis and phagocytosis of apoptotic bodies lead to the removal of unnecessary cells. In this phase, regression of many of the newly formed capillaries occurs, so that vascular density in the wound progressively decreases.
Interruptions, aberrancies, or lags in the process can lead to delayed wound healing or non-healing chronic wounds. Among the many factors which regulate the repair mechanisms, mechanical factors play a critical role during the healing process [Agha et al., 2011]. Also gravitational alterations can affect tissue repair: most of the studies on wound healing in μg conditions show delay and impairment in wound and fracture healing, mostly due to changes in the inflammatory and in remodeling phase [Delp, 2008; Radek et al., 2008].
Therefore, the possibility to carry out research in unloading conditions represents an unique tool to increase our knowledge on wound healing biomechanics and the role of gravity in the process.
Moreover, in the perspective of longer-term space missions, with a growing number of astronauts involved, wound healing must be regarded as a serious problem, because the risk of injury due to traumatic events or unexpected emergency surgery will increase while medical evacuation times to Earth will become incompatible with the urgency of implementing assistance procedures. Therefore, it is crucial to understand the impact of microgravity (μg) on the mechanisms underlying wound healing.
In the frame of these studies, we developed an in vivo model of wound healing based on leeches [Hirudo Medicinalis]. The model is obtained by performing a wound and a suture on the back surface of the animal. This invertebrate represents an interesting model, since the sequence of events occurring during the healing is similar as in vertebrates. Moreover, the leech is very resistant and, once nourished, can survive for some months without eating. For this reasons, it can be considered one the most suitable living beings to be used for experiments both in modeled and real μg, even during long-term space missions.
For the experiments in modeled μg, animals were anesthetized with a 10% ethanol solution. Surgical wounds (10 mm length, 2 mm depth) were performed on the dorsal surface of the animals (at about the 15th metamere) and sutured (DAFLON 4/0 wire). For the exposure to modeled μg, each leech was housed in a T25 flask filled with leech culture medium. μg was modeled by a Random Positioning Machine (RPM), rotation speed 60◦/s, about 10−3 × g. After exposure to modeled μg, animals were anesthetized again and fixed in formaldehyde 4%, then dissected. Differences in wound healing between animals exposed to unloading conditions and controls (1xg) were analyzed by morphological imaging of the wound (Fig. 1), histology, autofluorescence and immuno-fluorescence microscopy. The results demonstrated that modeled microgravity induces a significant delay in wound closure and repair processes as proved by altered epithelium formation and matrix organization.
In order to counteract the microgravity-induced impairment in wound healing, we assayed in the leech model the effect of biochemical (Platelet Rich Plasma) and physical (NIR laser radiation) factors known to promote tissue repair. PRP is a concentrate of growth factors (normally released by platelets upon activation) which is obtained by blood centrifugation. The use of red and infrared radiation to favor wound healing is documented in literature applied in clinics. Our previous studies have shown that NIR laser radiation improves the cell energy metabolism, favors the formation of endothelial cell monolayers, improves the production and assembly of ECM components as fibronectin, proteoglycans and collagen I [Monici et al., 2011].

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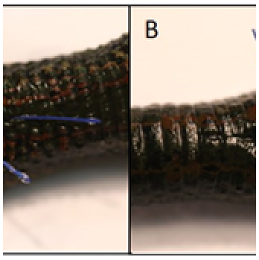
Figure Legend:
Fig.1 Effect of modeled microgravity (RPM) on in vivo model of wound healing. A Control; B Exposed to microgravity

Figure 1



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Keywords: Wound Healing, Hirudo medicinalis (Annelida), Microgravity (µg), Platelet rich plasma (PRP), NIR laser radiation, in vivo model

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