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Short Review

Translational Standardization of Partial-Thickness Burn Injury in Rats for Platelet-Derived Repair Studies

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Abstract

Comparing results of experimental burn trials between animals is complicated if the animals injure the tissue in the same manner, using different injury depths and injury severities. The scoping review, conducted by Kyriakopoulos, presented a detailed analysis of the manner in which a burn's depth is determined by nominal temperature & exposure time in conjunction with a variety of other factors, including: Pressure, contact stability, device geometry, site of burn, thermal equilibrium and histological confirmation timing. The primary focus of this article is to move from considering a methodological concern noted in the scoping review to using a standardized rat dorsal partial-thickness burn model for evaluating Platelet-Rich Plasma (PRP) and Platelet Lysate (PL). Controlled injury-generating variables in this model are temperature, duration of exposure and pressure/load of contact; while histology is used as an indicator for verifying whether or not a partial-thickness injury has been generated. Thus, within this controlled model, the administration of PRP/PL to patients following burn injury will allow for regenerative processes (epithelial repair, granulation tissue formation, inflammation and dermal remodeling) to be evaluated relative to a more precise baseline injury. Preliminary histological data comparing PL-treated to PL-untreated wounds at 7 and 10 days have revealed that PL-treated wounds demonstrate an orderly pattern of repair compared to controls, including: less epithelial detachment; more mature granulomatous tissue formation; and more mature epithelial structure. These initial observations will require further evaluation through blinded analysis and morphometric analysis, but they support the impact of burn-induction standardisation on regenerative medicine research. Pancreatic cancer is highly metastatic, and metastasis is the main cause of cancer-related deaths. Therefore, finding methods to inhibit pancreatic cancer metastasis has important clinical value. N-dihydro galactochitosan (GC) is an immunostimulant that can enhance the anti-tumor immune response to inhibit metastasis in combination with photothermal therapy. Here, we found that GC can inhibit the migration of pancreatic cancer cells through interactions with Caveolin-1 (Cav-1). The fluorescence of GC-FITC on the cell surface overlaps with Cav-1-Red, is enhanced by adCav-1, and is weakened by siCav-1, indicating that the localization of GC depends on Cav-1. GC inhibits the migration of malignant cells by blocking the signal transduction of Cav-1 and its downstream molecules. In an orthotopic pancreatic tumor model, GC can inhibit tumor metastasis in tumor-bearing mice. These results demonstrate GC's capacity to act as a partner in pancreatic cancer therapy and indicate future directions for metastatic cancer therapy.

Keywords: Partial-thickness burn, Sprague-Dawley rat, Burn standardization, Platelet-rich plasma, Platelet lysate, Histology, Re-epithelialization, Granulation tissue, Wound repair, Translational research

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Description

From methodological mapping to experimental use

The importance of the focal scoping review is that it modified the initial starting point of the discussions. In the majority of preclinical burn studies, researchers pay more attention to the intervention than to the burn injury which is considered a step in the procedure that has already been solved. The focal scoping review demonstrated that this is an unsafe assumption. The animal model of burn injury may be easy to replicate but may still be poorly standardized for therapeutic comparisons **[1]**. This is especially true for partial-thickness burn injuries where a small difference in the amount of viable dermis can significantly affect re-epithelialization, persistence of inflammation, conversion from burn wound to scar as well as the final scar pattern **[2-4]**.

Our research aims to provide an answer to a real-world question: Can we use PRP and PL in a rat model whose depth of burn has already been created before testing a biologic treatment? A dorsal partial-thickness burn model in Sprague-Dawley rats was developed with the goal of providing a reproducible way to develop PRP and PL treatments and utilize them for continued research. The contribution of this work was not to add another platelet-derived treatment to the literature, but rather to test the ability of platelet-derived treatment to aid in the repair of a wound where the depth of the wound had previously been established and verified histologically.

What the review required from the next model

It has been established through research that both contact time and temperature alone, create and do not, create enough injury when combined with other quantitative measures, such as force applied to skin, perpendicularity and stability of delivered thermal dose, geometry of heated surface and Inter-wall heating and skin contact time (between heating and skin contact) **[1,5]**. Although the scald, steam and radiant models each differ in terms of their dominant source(s) of variability; they produce various levels and types of injuries based solely on the exposure(s) delivered at the tissue interface level, and not just from a nominal exposure level **[1,6]**.

This has serious implications for PRP/PL study. If one group has a baseline burn that is slightly more superficial, healing may be incorrectly attributed to treatment. If one group has a baseline burn that is slightly deeper, there may be an important biological effect missed. It is important to consider that in rodents, macroscopic measurement of wound area is subject to contraction; thus, histology (microscopic measurements) should be a key outcome measurement when assessing both epithelial healing and dermal thickness at endpoints. This approach also conforms to general expectations of animal studies reporting detailed methodology that may impact reproducibility and interpretation **[7]**.

Design of the standardized partial-thickness rat model

The model was created using three variables identified as being of critical importance to contact burns: Temperature, exposure duration and pressure/load on the skin at the site of contact. A specially designed apparatus for the contact burn evaluation has been made to ensure that the operator's hand pressure, angle of application, time between burns and stability of applicator will have less effect on producing the injury than if applying the heated instrument manually. An example of this is two manually applied heated instruments that seem identical in appearance but created different injury depths due to very slight changes in the conditions under which they were applied.

First the pilot calibration helped confirm the injury categorization prior to comparing therapies. The histologic examination of the burn site was the anchor for developing the models. The model could only be considered appropriate for PRP/PL testing once the selected conditions demonstrated a partial-thickness pattern as opposed to simply assuming an injury on the basis of the selected device's setting. This step represents one of the key take-aways from our review; that is, standardisation is demonstrated in tissue, and not in the protocol sheet alone **[1]**.

This therapy is then utilized on the burn wound's defined injury tissue. Biological justification exists for the use of PRP and PL for burn healing since platelet-derived materials contain several important biological agents involved in angiogenesis, the activation of fibroblasts, the turnover of the extracellular matrix, keratinocyte movement to cover new skin, and the regulation of the inflammatory phase **[8-10]**. Therefore, administering PRP and PL at an appropriate time for injury during the early postburn period, (within 48 hours) is both clinically aligned, and biologically supported as the wound is experiencing the transition from active inflamed tissue to granulating and epithelialised tissue in its healing, while the burn depth will continue to be defined in the zone of stasis **[3,4]**.

Early histological observations

The initial parts of the standardized model should be seen as initial comparisons rather than evidence of efficacy. Nevertheless, they unify as to the recovery potential due to controlling the starting injury. Seven days after treatment, the untreated control wounds had basal-layer separation, small abscess-like foci of inflammatory reaction, a multilayered, and relatively atrophic epithelial structure and little mitotic activity, whereas the PL-treated had more granulation tissue evident and less epithelial separation.

The distinction on Day 10 in wound healing was primarily related to the maturation of the epithelium. In the control wounds, the formed epithelium was multilayered but immature and had few mitotic figures present compared to the intervention specimens, which showed a thinner more organized epithelium with bi-layered architecture, parakeratotic changes, and greater mitotic activity. Histological evaluation of the treated epidermis demonstrated that it was becoming more like reparative tissue than corresponding control tissue.

Caution must be exercised in the interpretation of these findings. In order to be considered as evidence of efficacy, the findings will need to be subjected to a blinded semi-quantitative pathology score, epithelial-thickness measurements, mitotic index quantification, inflammatory grade, collagen evaluation and preferably through a digital histomorphometry examination. Currently, however, they serve to demonstrate the feasibility of quantifying a platelet-derived repair signal on a burn wound that has been produced and tested with greater methodological rigor.

How the new data extend the scoping review

Metastasis remains a significant hurdle in cancer therapy and is associated with as many as 90% of all cancer-related mortalities **[1]**. Conventional therapies like surgery cannot prevent metastasis, while more robust therapies, like radiation and chemotherapy, carry harsh side effects and are resisted by certain type This scoping review has mapped variability across sources of empirical evidence. The current model has taken this information and applied it to the establishment of an experimental repair question. The extension of this work can be divided into three components. The first is the incorporation of operator-sensitive variables as described in the scoping review into the induction design, rather than discussing them post-hoc. Second, prior to interpreting the effects of PRP/PL, histological assessment of the burn depth will occur. Finally, through the initial evaluation period, outcome measures will not be limited to only surface closure; they will also include epithelial organization, inflammatory activity, and dermal repair.

Understanding this distinction is critical to translating results. The ability to determine the initial burn depth could provide evidence supporting positive effect as a factor. Moreover, knowing the initial burn depth will allow easier interpretation of the amount of variability in the final lesion (the value of neutrality) due to uncontrolled variability in the initial lesion. Therefore, the focus of the model not only tests PRP or PL, but also does so under conditions that will aid in the clinical interpretation of their biological effects.

Conclusion

The authors of the focal review indicated that experimental burn induction represents a reproducibility issue with significant ramifications for research on soft tissue repair **[1]**. This study of PLT-based burn repair in rats utilizes the findings from the focal review by controlling temperature, duration of exposure, and pressure/load; and anchoring injury in histopathology prior to evaluating the impact of PRP as compared to PLT in the animal model. The model will also provide answers to one of the major shortcomings of the previous literature. Based on histological data collected from preliminary days 7 and 10, it appears that PL-treated wounds have a greater likelihood of exhibiting a more organized pattern of early repair than does the contralateral non-treated group. While the data at this time do not yet provide enough evidence for a definitive therapeutic claim for PL, they do provide a basis for demonstrating the importance of standardization in methodology to make biological interpretation of the use of platelets as a therapeutic intervention more reliably valid. As such, the new experimental model is not independent from the scoping review; it is the continued experimental support for the primary conclusion of that review.

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