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Editorial

Pharmacological Characteristics of Granulation Tissue: a Key in Understanding the Wound Healing Phenomenon?

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Wounds are perhaps one of the oldest undesirable experiences in human history. The phenomenon of wound healing is a complicated scenario of interactions between an array of factors, including cell products (cytokines, growth factors, neurotransmitters, and various endogenous inflammatory mediators) as well as cellular activities (collagen synthesis, myofibroblast contraction) and interactions with other cells involved in inflammatory responses (such as mast cells, macrophages).

Healing has been and still is problem. In order to resolve this dilemma, many researchers have viewed this phenomenon from different prospectives to elucidate its nature and detangle the mystery behind it. Despite the great progress in controlling infected wound by use of antiseptics and administration of antibiotics, the wide spread presence of chronic and diabetic wounds has proved that these interventions have limited efficacies.

Among all fields of studies in which wound healing is a concern, pharmacological prospective seems to have a unique position. It facilitates our better understanding on the nature of receptors and how the wound behaves when manipulated pharmacologically. From pharmacological prospective, it seems to us that one way forward to resolve many of ambiguities surrounding the nature of wound healing process, is to study the wound pharmacologically. This can entail the use of both *in vivo* and *in vitro* models of wound healing and, ultimately, be tested clinically.

From pathological point view, myofibroblasts, the cells that are considered responsible for wound contraction where first introduced by Gabiani in 1971 [1]. These are differentiated cells that originate from resident fibroblasts in the fascia and seem to orchestrate the process of wound closure. This finding sparkled a new window in pharmacological research aiming to elucidate the nature of receptors and the behavior of, an ignored this tissue (the fascia), to pharmacological interventions.

The intact fascia, the transparent tissue covering almost all organs and is found under the skin of all mammalians, was considered, even in among pharmacologist community, as unresponsive to pharmacological interventions. However, pharmacological studies showed that the fascia, like many other tissues in the body, is responsive to pharmacological tests. However, these responses, like the tissue itself, are unique. It contracted to antihistamines such as mepyramine, diphenhramine, but weakly or non responsive to either acetylcholine or adrenaline. However, it responded strongly to adenosine. The responses, both qualitatively and quantitatively, were found to change when retested on the granulation tissues that are originated from the intact fascia. For example, when compared with intact fascia, the level of contraction to adenosine was found to increase almost 20 fold in the granulation tissues. The responses to andesine where also found to be much prolonged when compared to angiotensin (minutes versus seconds) [2].

It is generally agreed that *in vitro* models are very useful preliminary studies that spare animal use, and provide a range of useful data which pave the way for hypothesis development. These hypotheses need to be tested under both *in vivo* conditions in animal models and ultimately tested clinically. Therefore, in order to justify and correlate these findings and gaining better insight of this phenomenon, it is prudent that research works should report the results both types studies simultaneously.

Despite of these generally agreed scientifically proven principles; there is lack of a unified agreement as which method accurately reflects the true behavior of the wound healing process. The experimental methods used, as well as the results obtained from these varied. The *in vitro* models and the *in vivo* rate of wound closure used report different results. Which model, best reflects the wound is still a debatable subject. Some use fibroblast-embedded matrix models, while others used intact and granulation tissue superfusion methods [3]. In our view, whichever model is used, it should at least produce reliable consistent and repeatable measurements.

The *in vivo* wound closure studies have been a subject of controversies too [4]. The method of measurement of wound surface area, even how to present the results mathematically are still not agreed upon. Different animal models have been used for assessment of wound closure studies [5]. However, some studies suggested that the rat has the closest time scale of wound healing to human.

In order to minimize the inconsistencies in the results and be able to come to a reliable conclusion, pharmacologically speaking, we should appreciate that the wound tissue behaves differently in time of sampling fashion and is much influenced by the environmental conditions in which it is placed in. For example, an intact fascia or a wound granulation tissue will respond different to a pharmacological agent when subjected to different pH media, electrolyte and oxygen concentrations [4].

Future *in vitro* works showed attempt to elucidate the role of endogenous substance and attempt to manipulate or mimic the wound envenomed. These findings may then be extended to testing under *in vivo* conditions to assess the potential role of tested conditions in wound healing process.

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The field of wound healing is still a demanding one and we still need to go a long way to attain the goals of rapid scarless healed wound. Therefore, understanding the unique physiological, biochemical and pharmacological processes that govern this complicated scenario are essential prerequisite for learning how the wounds heal. In the intervening period, as Hunt has pointed out [6]: "If you learn to look further and if you learn to see anew" we may come to a gain better insight into this interesting and mysterious phenomenon.

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