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Review

Association of silk sericin and platelet lysate: Premises for the formulation of wound healing active medications

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ABSTRACT

Silk sericin (SS), a globular and water-soluble protein, showed to *in vitro* sustain the proliferation of different mammalian cell lines, and to *in vitro* protect them from the oxidative stress because of its free-radical-scavenging activity. Also, platelet-derived products, such as platelet gel, platelet rich plasma or platelet lysate (PL) are used in cell cultures as a serum substitute due to their great content of growth factors. In the clinical practice, both SS and PL were employed for various reparative treatments and showed to sustain the wound repair process regulating fibroblast recruitment, migration, proliferation and differentiation. For these reasons, the combination of PL and SS could lead to effective and innovative products, either for the *ex vivo* cell expansion, or for the production of active wound healing advanced medications.

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1. Wound healing and skin regeneration

The human body responds to injury by attempting to heal itself. Regenerative medicine accelerates this natural healing process by harnessing advances in physiology, pathology and pharmacology, to restore health and function of cells, tissues and organs compromised by disease, ageing or congenital defects [55].

Chronic non-healing wounds, including venous leg ulcers, diabetic foot ulcers, and pressure ulcers, affect the 1%–2% of the general population in developed countries, with an estimated cost of 96.8 billion per year [73]. After a skin lesion, a wound healing process, which consists of a highly organized and coordinated series of events, including inflammation, proliferation and remodelling, is started to restore tissue integrity and functions. This healing process requires the recruitment and activity of different cell types, such as native immune response cells, endothelial progenitor cells, keratinocytes and fibroblasts (Fig. 1).

Diabetes, bedsores, obesity and vascular diseases, to name few examples, can interrupt the healing process leading to the development of non-healing chronic wounds [66]. As in this context a therapeutic approach to repair or regenerate the tissue is needed [68], the traditionally-employed dressing materials, used to cover and thus protect wounds, have been substituted with modern wound dressings, also conceived to enhance the re-epithelialization, collagen synthesis and angiogenesis and/or to prevent infections [32]. Such modern medications are generally based on hyaluronic acid, alginate and chitosan [37] or other active substances (such as antibiotics), and recently great attention was dedicated also to other natural compounds, such as

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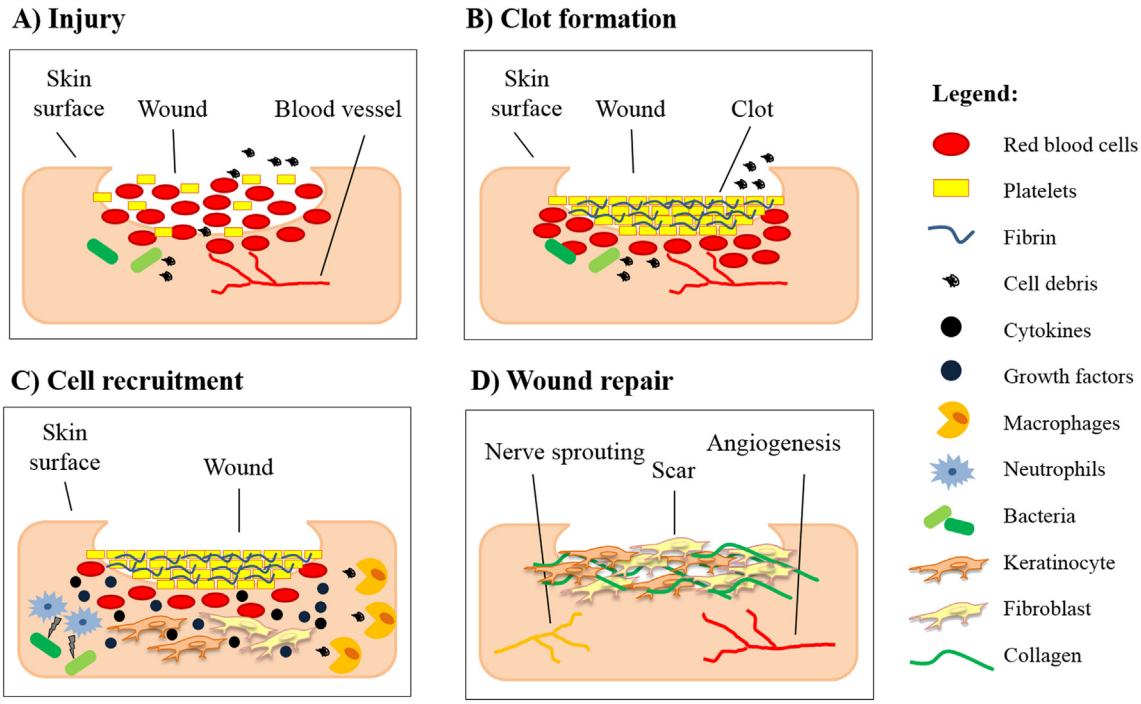

Fig. 1. The wound healing process. Wound healing is a complex process. (A) After the injury, bleeding occurs as a consequence of blood vessels damages and cell debris are released. Without the skin protection, bacteria penetrate into the wound. (B) A clot, made of platelets and fibrin fibres is formed to stop bleeding. (C) Platelets release a set of cytokines and growth factor which activate the immune response: neutrophils neutralize bacteria and macrophages phagocytes cell debris; also keratinocyte and fibroblast are attracted by the chemotactic gradient. (D) Keratinocytes and fibroblasts start the wound repair by deposition of collagen; angiogenesis leads to the formation of new blood vessels and nerve sprouting occurs.

microalgae extracts [7,22,31,46]. As a powerful tool of regenerative medicine, tissue engineering, thanks to the combined use of cells and biomaterials, become an attractive tool for skin repair and regeneration, especially when skin burn wound must be treated [91]. The current strategy for tissue engineering typically consists of *ex vivo* cell expansion, followed by their transplantation into damaged areas with the use of specific scaffolds based on biomaterials [69,70]. Consequently, important considerations on how cells are expanded and what type of biomaterials is used can be done. For the *ex vivo* cell expansion, fetal bovine serum (FBS) represents nowadays the gold standard as a medium supplement. In fact, FBS provides glucose, growth factors, proteins, lipids, minerals, vitamins, adhesion molecules and hormones necessary for cell growth and expansion. On the other hand, FBS has a poorly defined composition [87] and poses risk factors, as it may be a source of xenogenic antigens and zoonotic infections [1]. In order to reduce the concerns raised by the use of animal serum, several strategies have been proposed and led to the investigation of FBS substitutes. Among them, human blood materials and some natural compounds have been tested. In particular, platelet lysate (PL) has emerged as an effective medium supplement for the expansion of various cell types; other autologous or allogeneic human blood-derived materials, including human serum and plasma, have been tested, but they were not as promising as PL [44]. Among natural compounds, protein fractions isolated from plant extracts, called vegetal serum [42], have been tested on two different epithelial cell lines, demonstrating that they could be promising alternatives to serum [67]. Recently, also silk sericin (SS), a natural protein isolated from cocoons, which has been exploited in the last decades due to its remarkable properties, showed to be an effective alternative to FBS.

Biomaterials employed in tissue engineering have a pivotal role in the regenerative process: they do not act only as "filler" providing structural support for cell accommodation and attachment, but they also guide and sustain new tissue formation and maturation. In detail, smart materials for tissue engineering can regulate the functions of living cells in responding to changes in the surrounding microenvironment [89,90]. While several attempts have been made in pursuing the perfect synthetic biocompatible polymer, natural biomaterials have attracted considerable attention in the regenerative medicine field, and among them the ones derived from human blood. In fact, they are rich in growth factors and proved to be able to overcome many biological and technical problem correlated with synthetic biomaterials [23]. In this regard, due to their important features, both platelet lysate and sericin can be promisingly used to sustain tissue regeneration *in situ*.

In this review, authors point out the state of the art regarding PL and SS employment for regenerative purposes, starting from their employment as a medium supplement for the *ex vivo* expansion step, and highlighting their possible use as "active" to sustain *in situ* tissue regeneration, with particular emphasis to the wound healing process.

2. Platelet lysate

PL is the product obtained by platelet lysis. Platelets are corpuscular blood elements, which play an essential role in the regulation of hemostasis and in the clot formation during bleeding, but also in the wound healing and tissue regeneration processes. In case of tissue damage, the adhesion molecules exposed by the damaged endothelium (such as the von Willebrand factor, the collagen, the fibronectin and laminin) activate platelets that release growth factors previously stored in their α granules. This process triggers the tissue regeneration mechanism [59]. The same growth factors released in physiological conditions are useful for the production of cell culture supplements. PL production starts with platelet concentrate, that is prepared by two main methods, as summarized in Fig. 2A.

In the Platelet Rich Plasma (PRP) method, the whole-collected blood is centrifuged so that all the red blood cells separate downward from the mixture of plasma and platelets; the final platelet concentrate is collected and re-suspended in 50–70 ml of plasma. In the *Buffy Coat* procedure, blood is centrifuged to obtain a triple stratification: i) the top layer, made of plasma without cells; ii) the middle layer (the *Buffy Coat* one or

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