A living band-aid for epidermolysis bullosa

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Even though the basic premise for success in medicine is the need to understand the pathology before we can fix it, there are examples of clinical advances that have been accomplished without a full comprehension of the underlying mechanisms. For example, haematopoietic cell transplantation for leukaemia (to stay with blood, which is the dominant theme of this Journal) has been used to restore normal haematopoiesis after the malignant bone marrow was destroyed by high-dose chemotherapy. The reason this therapy is effective, and what was not realised early on, is that even though haematopoietic cell transplantation replaces the lymphohematopoietic system of the recipient, the major treatment benefit (especially in acute myelogenous leukaemia) actually comes from the immune clearance of leukaemic blasts by graft-versus-leukaemia reaction¹.

Although such interventions are valued to decrease the disease burden rather than to increase biological knowledge, sometimes the observations derived from using incompletely-defined measures have been instrumental in understanding the basic mechanisms of the treated condition. In this fashion, a response to therapy can both illuminate the pathology and suggest new means of clinically meaningful intervention.

The case report of Tadini et al.² in this issue of the Journal describes such an experience: the use of a biological product (umbilical cord blood platelet gel, CBPG) for local therapy in a life-threatening condition (dystrophic epidermolysis bullosa, DEB). DEB, a prototypical genodermatosis, is caused by mutations in the type VII collagen gene, COL7A1. Due to the diminished quantity and quality of type VII collagen protein, people with DEB develop severe mucocutaneous lesions. Typical pathophysiological and clinical consequences are the loss of the barrier function of the epidermis and resulting infections, fibrosis, and scarring. Individuals with DEB suffer excessively painful wounds that become chronic and, in many cases, lead to aggressive, fatal, squamous cell carcinoma³. Tremendous efforts are under way to apply cellular, gene, and protein therapy to make DEB a controllable disease, and yet to date there is no cure⁴-⁷.

Tadini et al. describe three individuals with severe chronic skin wounds secondary to DEB who responded favourably to local administration of allogeneic CBPG. The children were treated for 3 weeks and followed an additional 4 weeks. Importantly two similar lesions were identified in each child; one wound was treated with standard of care and the other with CBPG. In this fashion, each individual with DEB served as her/his own control. Remarkably, the CBPG-treated lesions re-epithelialized, and healthy-appearing skin covered the wounds. In addition to quantifiable changes in skin repair, the decrease in pain led to a better quality of their days and weeks, to more physical and intellectual mobility, and to a more hopeful outlook on life for these children and their families.

The first result of this study is that application of CBPG appears safe. One child experienced itching (itself common in DEB), but no clinically obvious, significant side effects were observed.

Further, this observation expands the potential use of platelet-rich plasma products in clinical practice. Although there is striking variability in source (autologous and allogeneic), standard operating procedure, dose, dosing, and route of administration, platelet-rich plasma has been used in orthopaedics (tendinopathy, osteoarthritis, musculoskeletal soft tissue injury), sports medicine (augmentation of tendon and articular cartilage repair), maxillofacial (osteonecrosis of the jaw, augmentation procedures of the maxillary sinus) and plastic surgery (reviewed in⁸). At least in part due to the extreme variation of approaches, most methodical analyses have found insufficient evidence to support use of platelet-rich plasma for relief of pain and to improve function⁹-¹³. In dermatology, the applications have been equally diverse: skin rejuvenation, hair transplants, diabetic ulcers, and burns, although with better (but not unanimous), statistically significant and clinically meaningful benefits¹⁴-¹⁶.

Lastly, and perhaps most importantly, this study adds momentum to the ongoing search for bioactive molecules with potential application in regeneration and tissue repair. Specific to CBPG, platelets contain numerous short-range biomolecules, such as fibrinogen, von Willebrand factor, factor V, P-selectin (in alpha granules), and serotonin, calcium and ADP/ATP (in dense granules). Platelet and plasma growth factors (such as fibroblast growth factors, tissue inhibitor of metalloproteinases, platelet-derived growth factors,
vascular endothelial growth factor, and transforming growth factor beta) can stimulate proliferation of dermal fibroblasts; vascular ingrowth; deposition of glycosaminoglycans, collagens, elastin and other components of extracellular matrix; recruitment of repair cells to the wound; and antimicrobial and pain-relieving effects. This physiologic capacity stimulates and accelerates wound healing, and is likely force-amplified as such growth factors are concentrated in the CBPG and delivered directly to the wound bed.

Despite the hope this research brings, it is somewhat tempered by the clinical reality of DEB, as it is unlikely that the reparative reactions observed after CBPG application will translate to permanent or even long-term benefits. CBPG preparations are unquestionably more functional, more physiologic, more elegant bandages than those currently in use, but DEB is a progressive, genetic, systemic disease that is unlikely to respond to surface or local therapy of any kind for very long. Also, despite the potential for rapid productive wound closure, the optimism may need to be qualified a little by the fact that children with DEB heal many of their wounds spontaneously and quickly, even though they are prone to re-injury and re-blistering at the same and other sites.

The true long-term impact of this work is in its potential to point out new paths for investigations that can illuminate the mechanisms of wound healing in DEB and suggest novel, more effective, treatment measures. In contrast to typical bandages, CBPG is composed of numerous biologically active molecules. These can function both as signals for recruitment of reparative cells, as well as sponges that limit the sometimes overwhelming inflammatory and pro-fibrotic responses that amplify the consequences of local trauma.

It is also likely that the potential of CBPG to stabilise DEB wounds can be further improved in combination therapy with recently identified long-range signals, for example, the high mobility group box 1 protein, which is relevant to regeneration in general and to wound repair in DEB in particular.

When combined with natural or synthetic polymers having the capacity to gradually, even sequentially, exude a cocktail of agents active in productive skin repair, and further enriched with the proteins absent in discrete disease states, (e.g., type VII collagen protein for people with DEB), it is possible to imagine CBPG as part of a bioengineered and customisable "living band-aid".

The Authors declare no conflicts of interest.

References