Platelet-rich plasma and the biological complexity of tissue regeneration

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I congratulate the International Olympic Committee consensus panel on having produced as clear a summary of the current understanding of the basic and clinical science relating to platelet-rich plasma (PRP) as the body of published literature allows. While there was initially great hope in sports medicine circles that PRP would become the magic bullet for injuries, recent trials such as that of de Vos et al have failed to provide the conclusive evidence so desired.

This is not surprising. The more we learn about tissue regeneration, the more apparent it becomes how complex a process it is. Tissue regeneration is not a passive phenomenon, instead it is a highly coordinated interplay of multiple cell lines at different stages of differentiation. Different cellular and humoral components play their different roles.

The process can be likened to the repair of a collapsed building. Consider muscle injury. The initial cells on the scene, due to bleeding, are platelets, but they appear to be relatively passively involved—alarm bells that sequester and awaken the major players. Platelets release chemotactic factors that attract neutrophils to clean the debris. However, within 24 h macrophages arrive, akin to the foreman, and it is these cells that appear to regulate the process from this point onwards. If there is any ‘brains’ or ‘thinking’ to repair work, it would seem to be the macrophages doing it. Next come the actual builders. Fibroblasts are activated to produce a collagen infrastructure, and satellite cells to form myocytes and finally myotubes, merging to become a single strand of muscle fibre.

So where do ‘growth factors’ come into it? These proteins are simply the communications being sent between the foreman and his workers. The messages are very simple—move or stay put, divide or do not divide, live or die, make collagen, etc. In biology we use the terms chemotaxis, mitosis, quiescence, apoptosis and protein biosynthesis.

The point is this—growth factors are just the messenger molecules used by one cell to send an instruction to another, they are not the person giving the orders.

Unfortunately the ‘language’ of growth factors is very different to English. We are used, pretty much, to one word having roughly one meaning. However, growth factor ‘words’ are more like a tonal language, Mandarin. In these languages the same word can have multiple different meanings depending on how you pronounce it. In the same manner, growth factors can produce varying effects depending on their concentration, time of release, point in cell cycle and recipient cell. Therefore, trying to pin any one growth factor down to one particular action can be pointless—transforming growth factor β1 is commonly associated with fibrosis, but it can stimulate regeneration or fibrosis, chemoattraction or stasis, depending on its concentration, target cell, and sequence within the tissue regeneration process.

Moving back to the analogy, it requires a great deal of intelligence to rebuild a collapsed building. The foreman has to send and receive accurate messages, at the right time and to the right people, otherwise the building will end up with structural flaws, and will probably fall down again. Imagine if he simply threw the blueprints in the air, and allowed the workers to pick up a piece each and act on what it said—complete chaos! In the same way macrophages coordinate a complex interplay between themselves and fibroblasts/satellite cells.

This is where PRP has the potential to fall down. PRP has variable and inconsistent content and concentration. There is no consensus on the timing of the injection. What does a random bolus injection into an injury achieve? Are we sending these effector cells a clear and coordinated set of instructions with PRP? Or are they being sent a completely confusing message? It would seem hopelessly optimistic and naive to presume that we are accurately reproducing biological complexity.

PRP has shown promise in promoting accelerated scar tissue formation in dental grafts and wound healing, in which the regeneration of complex tissue is not a goal. In sports medicine, however, we require restoration of functional tissue—contractile muscle or tendon of high tensile strength—tissue of much greater complexity. The successes in maxillofacial applications are perhaps not analogous to these situations.

Whether or not PRP is eventually proved or disproved in sports injuries, it is nevertheless a good start. The sports medicine world has woken to the possibilities of regenerative medicine, and is trying to be scientific in the development of novel therapies. In the future we will have improved understanding of how the complex and overlapping processes of tissue regeneration are controlled by coordinating cells, stem cells, effector cells and the messenger molecules that they employ, and more importantly, how to manipulate these processes for a beneficial effect.

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