

Soft Tissue Repair and Healing Review

Introduction

The inflammatory and repair processes are no longer simple events to describe in the light of the ever increasing knowledge in this field. This review is only a brief resume of the salient events associated with tissue repair, particularly concerning the soft tissues. For further information, the reader is referred to recent reviews listed at the end of the paper.

Tissue healing (or tissue repair) refers to the body's replacement of destroyed tissue by living tissue (Walter and Israel 1987) and comprises two essential components - Regeneration and Repair. The differentiation between the two is based on the resultant tissue. In **REGENERATION**, specialised tissues is replaced by the proliferation of surrounding undamaged specialised cells. In **REPAIR**, lost tissue is replaced by granulation tissue which matures to form scar tissue. This review concentrates on the events and processes associated with the repair process.

Probably the most straightforward way to describe the healing process is to divide it up into broad stages which are not mutually exclusive and overlap considerably. There are several different ways to 'divide up' the entire process, but the allocation of 4 phases is common and will be adopted here – these being **BLEEDING**, **INFLAMMATION**, **PROLIFERATION** and **REMODELLING**.

In addition to the well established texts (Walter and Israel, 1987; Hardy, 1989; Peacock, 1984) some more recent and detailed texts can be found at Serhan et al, 2010; Granger and Senchenkova, 2010; Pitzer, 2006; Broughton et al, 2006). The key information in this paper has been previously published in Watson, 2003; 2006.

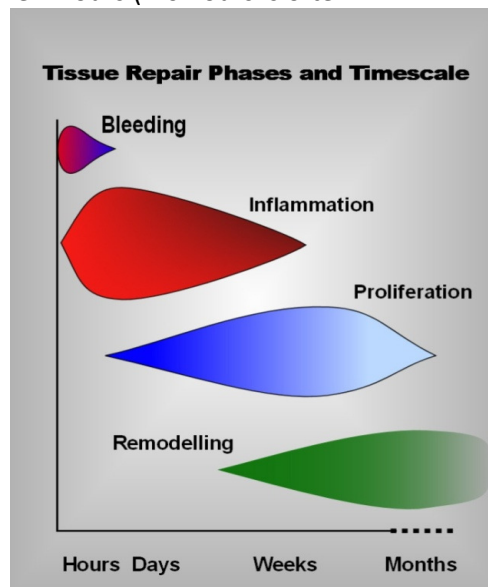
Overview

A brief overview of each phase is presented here before considering them in any detail. Figure 1 refers to a general arrangement of the phases.

BLEEDING PHASE

This is a relatively short lived phase, and will occur following injury, trauma or other similar insult. Clearly if there has been no overt injury, this will be of little or no importance, but following soft tissue

injury, there will have been some bleeding. The normal time for bleeding to stop will vary with the nature of the injury and the nature of the tissue in question. The more vascular tissues (e.g. muscle) will bleed for longer and there will be a greater escape of blood into the tissues. Other tissues (e.g. ligament) will bleed less (both in terms of duration and volume). It is normally cited that the interval between injury and end of bleeding is a matter of a few hours (4-6 hours is often



though this of course is the average duration after the average injury in the average patient. Some tissues may continue to bleed for a significantly longer period, albeit at a significantly reduced rate.

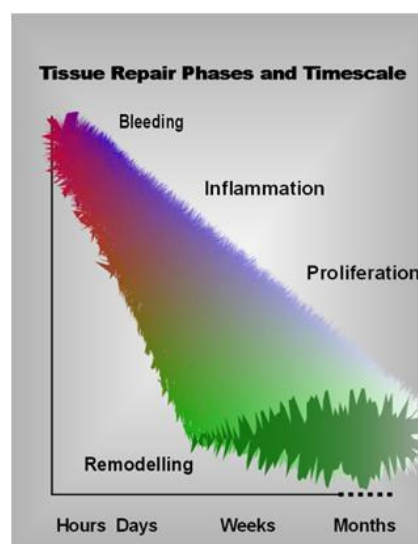


Figure 1(above) is a gross representation of the key phases of the tissue repair process. The phases identified are shown as separate entities, though in reality, they are interlinked in a very deliberate way. There are events

associated with one phase that act as stimulants for the following phase. Some examples of these have been included in the main text. Figure 2 (above) indicates the integrated reality of repair rather than the 'convenient' separate phase model.

INFLAMMATORY PHASE : OVERVIEW

The inflammatory phase is an **essential component** of the tissue repair process and is best regarded in this way rather than as an 'inappropriate reaction' to injury. There are, of course, numerous other initiators of the inflammatory process (e.g. repetitive minor trauma, mechanical irritation), though for the purpose of this paper, the injury model will be adopted. The inflammatory phase has a rapid onset (few hours at most) and swiftly increases in magnitude to its maximal reaction (1-3 days) before gradually resolving (over the next couple of weeks). It can result in several outcomes (see below) but in terms of tissue repair, it is normal and essential. The onset and resolution are swifter in more vascular tissues and slower in the relatively poorly vascularised tissues. The alternative initiators of the inflammatory events include mechanical irritation, repeated minor trauma, excessive heating and cooling plus others that may be less significant in therapy such as infection and a wide range of autoimmune disorders. The inflammatory events are essentially the same whichever 'route' is relevant for the initiation.

PROLIFERATION PHASE : OVERVIEW

The proliferative phase essentially involves the generation of the repair material, which for the majority of musculoskeletal injuries, involves the production of scar (collagen) material. The proliferative phase has a rapid onset (24-48 hours) but takes considerably longer to reach its peak reactivity, which is usually between 2-3 weeks post injury (the more vascular the tissue, the shorter the time taken to reach peak proliferative production). This peak in activity does not represent the time at which scar production (repair) is complete, but the time phase during which the bulk of the scar material is formed. The production of a final product (a high quality and functional scar) is not achieved until later in the overall repair process. In general terms it is usually considered that proliferation runs from the first day or two post injury through to its peak at 2-3 weeks and decreases thereafter through to a matter of several months (typically 4-6) post trauma.

REMODELLING PHASE : OVERVIEW

The remodelling phase is an often overlooked phase of repair in terms of its importance, especially in the context of therapy and rehabilitation. It is neither swift nor highly reactive, but does result in an organised, quality and functional scar which is capable of behaving in a *similar* way to the parent tissue (that which it is repairing). The remodelling

phase has been widely quoted as starting at around the same time as the peak of the proliferative phase (2-3 weeks post injury), but more recent evidence would support the proposal that the remodelling phase actually starts rather earlier than this, and it would be reasonable to consider the start point to be in the first week.

The final outcome of these combined events is that the damaged tissue will be repaired with a scar which is not a 'like for like' replacement of the original, but does provide a functional, long term 'mend' which is capable of enabling quality recovery from injury. For most patients, this is a process that will occur without the need for drugs, therapy or other intervention. It is designed to happen, and for those patients in whom problems are realised, or in whom that magnitude of the damage is sufficient, some 'help' may be required in order to facilitate the process. It would be difficult to argue that therapy is 'essential' in some sense. The body has an intricately complex and balanced mechanism through which these events are controlled. It is possible however, that in cases of inhibited response, delayed reactions or repeated trauma, therapeutic intervention is of value.

It would also be difficult to argue that there was any need to change the process of tissue repair. If there is an efficient (usually) system through which tissue repair is initiated and controlled, why would there be any reason to change it? The more logical approach would be to **facilitate** or **promote** the normality of tissue repair, and thereby enhance the sequence of events that take the tissues from their injured to their 'normal' state. This is the argument that will be followed in this paper – the promotion of normality, rather than trying to achieve a better normality.

If the tissue repair process is slowed, stalled or in some way delayed, encouraging the 'normal' sequence is the best evidenced way forward. This can be achieved with the same essential techniques as those used for a 'normally' progressing repair sequence, though it may take a 'stronger' or more 'intense' therapy to initiate a tissue response.

The mechanism through which therapy can be effective throughout the repair sequence is becoming better understood, though as a general comment, these effects appear to be achieved by 'stimulating' rather than 'changing' the events.

Inflammatory Events

Inflammation is a normal and necessary prerequisite to healing (Hardy 1989; Serhan et al 2010). Following the tissue bleeding which clearly will vary in extent depending on the nature of the damage, a number of substances will remain in the tissues which make a contribution to the later phases. Fibrin and fibronectin form a substratum which is hospitable to the adhesion of various cells.

The complex chemically mediated amplification cascade that is responsible for both the initiation and control of the inflammatory response can be started by numerous events, one of which is trauma. Mechanical irritation, thermal or chemical insult, and a wide variety of immune responses are some of the alternative initiators, and for a wide range of patients experiencing an inflammatory response in the musculoskeletal tissues, these are more readily identified causes. For the purposes of this review, only the traumatic route will be pursued though the key events and control systems involved in an inflammatory response subsequent to mechanical irritation etc are all but identical.

There are two essential elements to the inflammatory events, namely the **vascular** and **cellular** cascades. Importantly, these occur in parallel and are significantly interlinked. Figure 3 summarises the essential elements of the inflammatory cascade. The chemical mediators that make an active contribution to this process are myriad. They are usefully summarised in several reviews including Jiminez and Jiminez, (2004) and Singer and Clark (1999). Whilst these are clearly not the newest reviews, they do provide a useful background to the topic. Smith et al (2008) provide a useful review of the mediators associated with muscle injury, whilst Molloy et al (2003) have reviewed the role of these mediators in relation to ligament and tendon injury. In recent years, the identification of numerous 'growth factors' had led to several important discoveries and potential new treatment lines (e.g. Wagner et al 2003; Leung et al 2006).

VASCULAR EVENTS

In addition to the vascular changes associated with bleeding, there are also marked changes in the state of the intact vessels. There are changes in the calibre of the blood vessels, changes in the vessel wall and in the flow of blood through the vessels. Vasodilation follows an initial but brief vasoconstriction and persists for the duration of the inflammatory

response. Flow increases through the main channels and additionally, previously dormant capillaries are opened to increase the volume through the capillary bed.

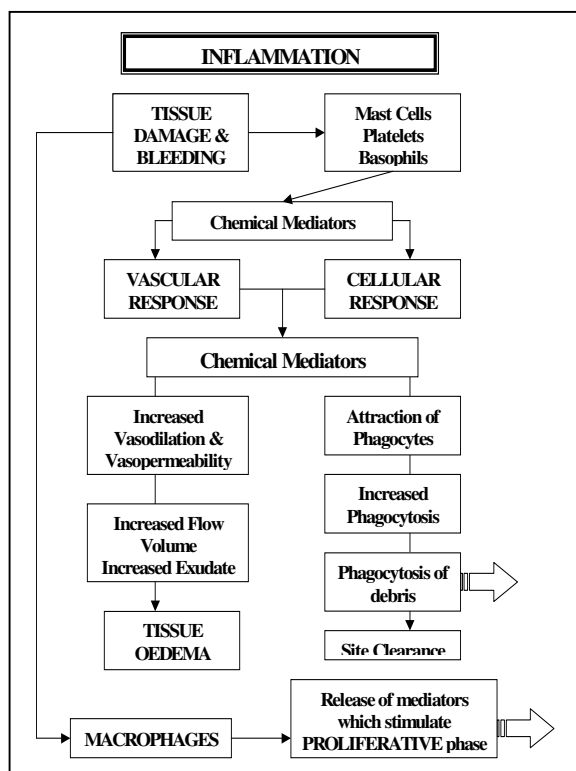


Figure 3 : Key Inflammatory elements

The cause of this dilation is primarily by chemical means (histamine, prostaglandins and complement cascade components C3 and C5 and many others) whilst the axon reflex and autonomic system may exert additional influences. There is an initial increase in velocity of the blood followed by a prolonged slowing of the stream. The white cells marginate, platelets adhere to the vessel walls and the endothelial cells swell.

In addition to the **vasodilation** response, there is an increase in the **vasopermeability** of the local vessels (also mediated by numerous of the chemical mediators), and thus the combination of the vasodilation and vasopermeability response is that there is an increased flow through vessels which are more 'leaky', resulting in an increased exudate production.

The flow and pressure changes in the vessels allows fluid and the smaller solutes to pass into the tissue spaces. This can occur both at the arterial and venous ends of the capillary network as the increased hydrostatic pressure is sufficient to overcome the osmotic pressure of the plasma

proteins. The vessels show a marked increase in permeability to plasma proteins. There are several phases to the permeability changes but essentially, there is a separation of the endothelial cells, particularly of the venules, and an increased escape of protein rich plasma to the interstitial tissue spaces. The chemical mediators responsible for the permeability changes include histamine, serotonin (5-HT), bradykinin and leukotrienes together with a potentiating effect from the prostaglandins.

The effect of the **exudate** is to dilute any irritant substances in the damaged area and due to the high fibrinogen content of the fluid, a fibrin clot can also form, providing an initial union between the surrounding intact tissues and a meshwork which can trap foreign particles and debris. The meshwork also serves as an aid to phagocytic activity (see below). Mast cells in the damaged region release hyaluronic acid and other proteoglycans which bind with the exudate fluid and create a **gel** which limits local fluid flow, and further traps various particles and debris (Hardy 1989).

CELLULAR EVENTS

The cellular components of the inflammatory response include the early emigration (within minutes) of the phagocytes (neutrophils; polymorphonucleocytes or PMN's) from the vessels. This is followed by several other species leaving the main flow, including monocytes, lymphocytes, eosinophils, basophils (Lorena et al 2002) and smaller numbers of red cells (though these leave the vessel passively rather than the active emigration of the white cells). Monocytes once in the tissue spaces become macrophages (Forrest 1983). The main groups of chemical mediators responsible for chemotaxis are some components of the complement cascade, lymphokines, factors released for the PMN's and peptides released from the mast cells in the damaged tissue (Egozi et al 2003, Vernon-Roberts 1988).

The PMN escapees act as early debriders of the wound. Numerous chemical mediators have been identified as having a chemotactic role, for example, PDGF (platelet derived growth factor) released from damaged platelets in the area. Components of the complement cascade (C3a and C5a), leukotrienes (released from a variety of white cells, macrophages and mast cells) and lymphokines (released from polymorphs) have been identified (see Walter and Israel 1987; Vernon-Roberts 1988; Dierich et al 1987; Smith et al 2008)

These cells exhibit a strong phagocytic activity and are responsible for the essential tissue debridement role. Dead and dying cells, fibrin mesh and clot residue all need to be removed. As a 'bonus', one of the chemicals released as an end product of phagocytosis is lactic acid which is one of the stimulants of proliferation – the next sequence of events in the repair process.

The inflammatory response therefore results in a vascular response, a cellular and fluid exudate, with resulting oedema and phagocytic activation. The complex interaction of the chemical mediators not only stimulates various components of the inflammatory phase, but also stimulates the proliferative phase. The course of the inflammatory response will depend upon the number of cells destroyed, the original causation of the process and the tissue condition at the time of insult.

INFLAMMATORY OUTCOMES

Resolution is a possible outcome at this stage on condition that less than a critical number of cells have been destroyed. For most patients that come

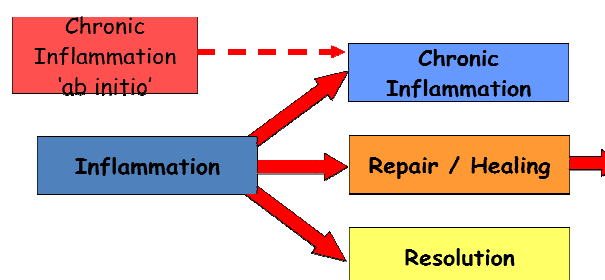


Figure 4 : Inflammatory Outcomes

to our attention, this is an unlikely scenario unless tissue irritation rather than overt damage is the initiator. There is some considerable debate with regard 'micro injury' or 'micro trauma' and whether it leads to a repair event or a resolution. It is possible that they should result in a micro repair, and if the tissues fail to respond in this way, the microdamaged tissue fails to mount a repair response, thus resulting in accumulative damage and possible longer term issues. This debate continues with interesting evidence e.g. Rompe et al, 2008; Frick and Murthy, 2010; Taljanovic et al, 2011).

Suppuration, in the presence of infective micro-organisms will result in pus formation. Pus consists of dead cell debris, living, dead and dying polymorphs suspended in the inflammatory

exudate. Clearly the presence of an infection will delay the healing of a wound (Zederfelt 1979).

Chronic inflammation does not necessarily imply inflammation of long duration, and may follow a transient or prolonged acute inflammatory stage (Vernon-Roberts 1988). Essentially there are two forms of chronic inflammation : either the chronic reaction supervenes on the acute reaction or may in fact develop slowly with no initial acute phase (ab initio) (Hurley 1985). Chronic inflammation ab initio can have many causes including local irritants, poor circulation, some micro-organisms or immune disturbances. Chronic inflammation is usually more productive than exudative - it produces more fibrous material than inflammatory exudate. Frequently there is some tissue destruction, inflammation and attempted healing occurring simultaneously (Hurley 1985, Walters and Israel 1987).

Healing/ Repair by fibrosis will most likely be taking place in the tissue repair scenario considered here. The fibrin deposits from the inflammatory stage will be partly removed by the fibrinolytic enzymes (from the plasma and PMN's) and will be gradually replaced by granulation tissue which becomes organised to form the scar tissue. Macrophages are largely responsible for the removal of the fibrin, allowing capillary budding and fibroblastic activity to proceed (proliferation). The greater the volume of damaged tissue, the greater the extent of, and the greater the density of the resulting scar tissue. Chronic inflammation is usually accompanied by some fibrosis even in the absence of significant tissue destruction (e.g. Hurley 1985; Li et al, 2007)

The effects of acute inflammation are largely beneficial. The fluid exudate dilutes the toxins and escaped blood products include antibodies (and systemic drugs). The fibrinogen forms fibrin clots providing a mechanical barrier to the spread of micro-organisms (if present) and additionally assists phagocytosis. The gel like consistency of the inflammatory exudate also makes a positive contribution by preventing the spread of the inflammatory mediators to surrounding, intact tissues. Transportation of invading bacteria (if present) to the lymphatic system stimulates an immune response whilst the increased blood flow contributes to the increased cell metabolism necessary for the proliferative stage by increasing local oxygen content, supply of necessary nutrients and removal of waste products. The leucocytes provide a mechanism for the phagocytosis of foreign

material, bacteria, dead cells, with the neutrophils (PMN's) and monocytes (becoming macrophages) making the greatest contribution.

There are several detrimental aspects of inflammation which deserve mention. Firstly the increased local hydrostatic pressure from the oedema can restrict blood flow if the injured tissue space is limited, produce pain and therefore limit function and additionally reduce local oxygen levels. There have been suggestions that free radicals produced as a result of acute inflammatory responses may have detrimental effects on cell membrane processes as may overproduction of lysosomal enzymes from PMN activity.

There are many aspects of the inflammatory events that can be influenced by therapeutic intervention, ranging from the mechanical to the biochemical. There is a growing body of evidence to support the effects of manual and exercise therapy on the 'soup' of chemical mediators, cytokines and growth factors. Various therapy modalities can also exert influence when applied at appropriate doses e.g.

- Ostrowski et al (2000) – link between exercise and Interleukin-6 (IL-6) production
- Leung et al (2006) – link between ultrasound and TGF- β in knee ligament healing
- Zhang et al (2004) – demonstrated link between electroacupuncture and peripheral inflammatory responses
- Bjordal et al (2006) – link between laser therapy and altered prostaglandin levels in the tissue (Achilles tendon)
- McBrier et al (2007) – link between US and Mechano Growth Factor (MGF)
- Nussbaum and Locke (2007) – link between US and Heat Shock Proteins
- Caltrioni et al (2008) – link between exercise and plasma glycosaminoglycan levels
- Li et al (2004) Mechanical stretching and fibroblast behaviour

In addition to the 'classic' modalities in this regard, it remains possible that small (endogenous) electric currents can exert an influence (e.g. Watson, 2008). The application of microcurrent based therapies is thought to enhance this component of the inflammatory/repair sequence (e.g. Poltawski and Watson, 2009)

Proliferative Events

The repair process restores tissue continuity by the deposition of repair (scar) tissue. This is initially granulation tissue which matures to form scar tissue. Repair tissue is a connective tissue distinct right from the onset in several ways from the connective tissue native to the site (Forrest 1983). Interesting recent developments have identified that in muscle there is a degree of regenerative activity post trauma, linked to the activation of a mechanosensitive growth factor and subsequent activation of muscle satellite (stem) cells (Hill et al 2003). A range of growth factors have been identified as being active in the processes of proliferation, leading again to some new potential treatments (e.g. Hildebrand et al 1998). The source of the majority of these cytokines is the inflammatory phase, thus 'turning off' or limiting the inflammatory events also reduces the signal strength stimulating these proliferative events.

Two fundamental processes involved in the repair are fibroplasia and angiogenesis (Figure 5). The function of the fibroblast is to repair the connective tissue (Venable 1989).

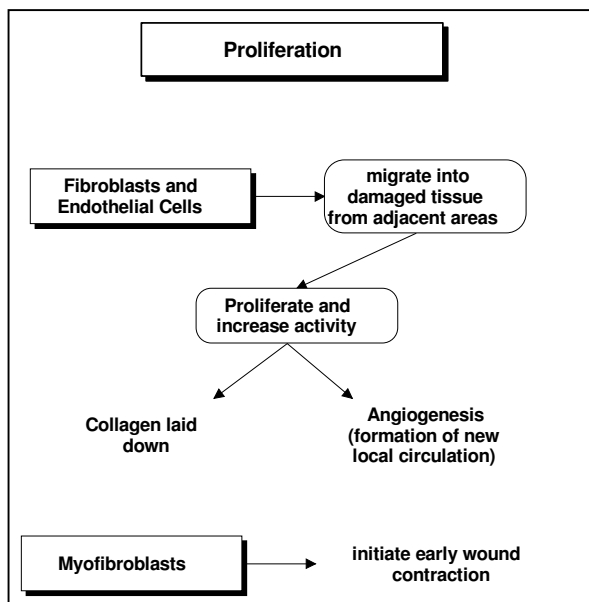


Figure 5 : Key Proliferative elements

Fibroblasts appear to migrate to the area from surrounding tissue. Fibroblastic activation appears to be chemically mediated, particularly by chemicals released from the macrophages during the inflammatory stage. Fibroblasts migrate into the damaged area and proliferate within the first few days after the tissue damage. Macrophage Derived Growth Factors (MGDF's) are a complex group of mediators responsible, at least in part for the activation of fibroblasts.

Alongside the fibroblastic activation, capillaries in the region of the tissue damage bud and grow towards the repair zone. Loops and arcades are formed together with anastomoses which re-establish a blood flow through the region, providing oxygen and nutrients whilst removing metabolic and repair waste products. Oxygen is critical for many of the reparative processes, but especially for collagen production (Venable 1989, Niinikoski 1980). A wide range of growth factors and chemical mediators have been identified which exert influences on the developing capillaries. These include macrophage derived factors, PDGF, lactic acid and fibroblast growth factor (Vernon-Roberts 1988). Some of these mediators are produced during the inflammatory phase, thus making an essential link between the inflammatory and proliferative phases. Growing evidence that various therapies are able to (positively) influence these proliferative and angiogenic events include :

- Azuma et al (2001) demonstrate that LIPUS influences angiogenesis in relation to fracture healing.
- Reher et al (2002) demonstrate influence of ultrasound in relation to NO and PGE2 production.
- Zhao et al (2004) demonstrate link between electrical stimulation and angiogenic enhancement by means of VEGF mediated response.
- Fitzsimmons et al (2008) demonstrate link between pulsed electric fields, chondrocyte activity and nitric oxide pathways .
- Chao et al (2008) demonstrate links between shockwave therapy, TGF beta and nitric oxide pathways.
- Rego et al (2010) ultrasound stimulation of prostaglandin (PGE₂) synthesis.
- Cheung et al (2011) ultrasound (LIPUS) and angiogenesis in osteoporotic fractures
- Kuo et al (2009) shockwave therapy increases several cytokines including VEGF in a wound healing model
- Bossini et al (2009) demonstrate the influence of laser therapy on the angiogenic events in wound repair
- Lu et al (2008) ultrasound (LIPUS) and VEGF regulation in fracture healing

Granulation tissue invasion follows the 'demolition' phase (when autolytic enzymes are released from PMN's and dead cells) (Walter and Israel 1987). The activation of fibroblasts and capillary budding would normally occur by about the third day after the tissue insult. The combination of capillary budding and collagen production results in a more vascular than usual repair site. The fibroblasts initially produce

predominantly type III collagen which will become type I collagen as the repair matures – during remodelling (Walter and Israel 1987). Fibroblasts also produce fibronectins and proteoglycans which are essential components of the ground substance (Figure 5) (Walter and Israel 1987, Forrest 1983, Hardy 1989).

Myofibroblasts are derived from fibroblasts activated by a variety of chemical mediators, and are responsible for wound contraction and the early strength of the repair. They draw the edges of the wound together, thus reducing the size of the final scar (Gabbiani 2003, Lorena et al 2002, Peacock 1984, Hardy 1989).

Granulation tissue matures with lymphatic development (in much the same way as capillary development), nerve fibre ingrowth and mast cell invasion. Collagen fibres are oriented in response to local stress thus providing tensile strength in the required directions (see Forrest 1983 and Hardy 1989 for useful collagen reviews). As the granulation tissue matures, there is a process of devascularisation with obliteration of the lumen of the vessels.

Remodelling Events

The remodelling phase primarily involves the refinement of the collagen and its associated extracellular matrix. The initial deposition of collagen produces relatively weak fibrils with random orientation. With maturity, the collagen becomes more obviously oriented in line with local stresses

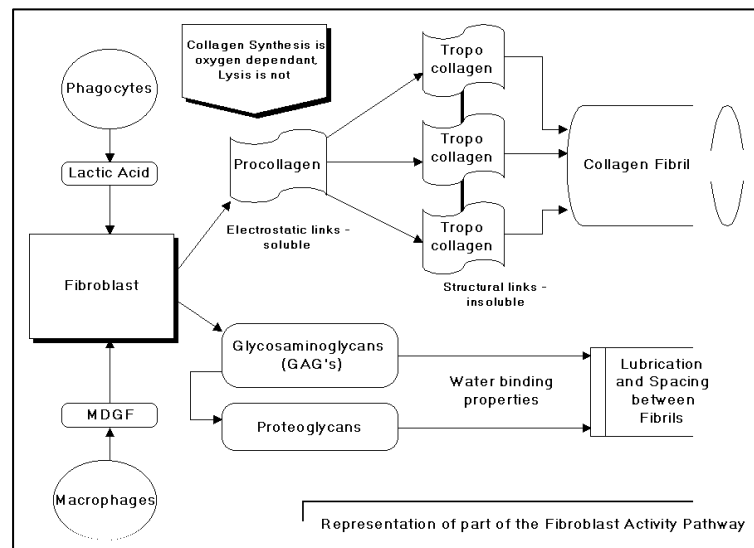


Figure 6 : Fibroblast activity during proliferation

(Culav et al 1999, Gomez et al 1991). A proportion of the original fine (Type III) collagen is reabsorbed (due to the action of collagenases) and is replaced with Type I collagen with more cross links and greater tensile strength (Vanables 1989, Forrest 1983). Collagen synthesis and lysis both occur at a greater rate in a normal wound compared with non

wounded tissue as old fibrous tissue is removed and new scar tissue is laid down. The maturing scar is therefore a dynamic system rather than a static one. There are several influential factors during this long phase, including physical stress. This remodelling process is initiated whilst the proliferative stage proceeds, therefore providing a considerable overlap between the phases. Final remodelling may continue for months, and possibly over a year beyond the obvious healing of the damage. See Hardy (1989) for a comprehensive consideration of collagen behaviour in remodelling and Culav et al 1999 for an excellent review of collagen and its roles). The potential mechanism by which physical stress can influence cell and tissue behaviour is usefully considered by Ingber (2003, 2008). Kahn and Scott (2009) provide a more recent paper linking mechanical stress and tissue repair whilst Mackey et al (2008) also provide a valuable review.

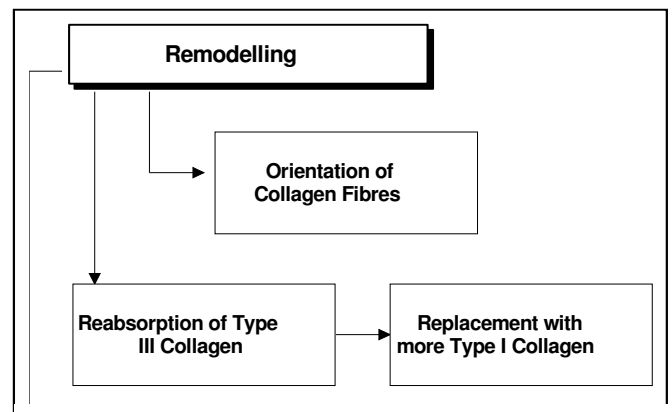


Figure 7 : Principal events of remodelling

FACTORS KNOWN TO DELAY HEALING are divided into general and local:

General: Age, Protein deficiency, Low Vitamin C levels, Steroids & NSAID's (inhibitory effect), Temperature (lower rate when colder)

Local: Poor blood supply / ischaemia, Adhesion to bone or other underlying tissue, Prolonged inflammation, Drying of the wound, Excessive movement or mechanical stress (restarts inflammation)

THERAPY INFLUENCES :

Clearly the effects of the whole range of therapies can not be considered in any significant detail here but in principle a therapy which is beneficial to the repair events is a therapy which stimulates rather than 'changes' the natural sequence. Promoting or stimulating the inflammatory events is not intended to achieve a 'bigger' inflammatory response, but to maximise its efficiency. Similarly, if delivering therapy during the proliferative phase, there would be no benefit in simply creating a bigger volume of scar tissue. The advantage of appropriate intervention is that it stimulates a maximally efficient response, and therefore the required repair material is generated with best quality and minimal time. In the remodelling phase, the refinement of the scar tissue is the aim and the use of therapy can have a significant effect, especially given the growing body of evidence relating the effects of mechanical stress and collagen behaviour.

Inappropriate therapy at any stage is perfectly capable of inhibiting these events and therefore results in a less good repair – therapy is not guaranteed to be beneficial – one has to be mindful of the events needed and be selective of the most appropriate (evidenced) therapy at each stage.

The other interesting recent development is that there is an increasing body of knowledge which supports the idea that existing therapies have an effect on the chemical environment of the repairing tissue (Watson, 2011). Exercise therapy, manual therapy and various modalities in electrotherapy are now known to exert such effects. This need not 'replace' the current explanations for the mode of action of therapy, but do offer an extended effects model in which there are mechanical, neurological, gross physiological, chemical and bioelectric effects of therapy. The mode of action of those therapies, historically employed, is actually a lot more complex

than was originally conceived and hitherto understood.

Conclusion : Tissue healing is a complex and dynamic system which enables effective repair of damaged tissue. The repair control system and links between its various components are complex, and there is an ever increasing volume of literature which continues to identify new mediators, cytokines and variants. Whilst this knowledge base continues to expand, the links between the effects of therapy and these chemical control systems is also growing.

There is little doubt that appropriate therapy has the capacity to influence the process in a positive way and the most logical and best evidenced approach to intervention is to stimulate or promote the 'normal' events rather than trying to change them to something better. If repair is underway, then keep it moving. If it is delayed, then stimulate it in order to help get it back on track. Whilst there are myriad approaches, those that are most effective appear to follow this philosophy.

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