

The formation of scar tissue is a normal part of wound healing, in response to injury, whether traumatic or surgically induced.

There is a 3-phase repair process: (1) inflammatory, (2) transitional repair and (3) maturation.

Following tissue injury, the initial event involves vascular changes: a brief period of vasoconstriction followed by vasodilatation and at the same time haemocoagulation.

This achieves a number of goals:

control of bleeding, establishing a mechanical barrier against infection, the apposition of wound margins, and setting up a biological framework within which wound repair may progress.

Another early aspect of wound healing, modulated by inflammatory cells, involves vasodilatation and an increase in blood vessel permeability permitting the influx of agents involved in wound healing.

A crucial role is played by histamine, polypeptides and prostaglandins in activation of blood vessel contractile proteins.

Most cells in injured tissue release histamine, which causes brief vasodilatation in adjacent blood vessels.

A combination of whole blood exudate and serous transudate creates the typical reddened, hot, swollen, painful area (the cardinal signs of inflammation are dolor: pain, rubor: redness, calor: heat, tumor: swelling).

Bradykinins, derived from plasma in the area of the injury, contribute to more prolonged vascular permeability.

Prostaglandins, produced by all cells in the body, are released with any breach of cell membrane integrity.

Some prostaglandins further contribute to long-term vascular vasodilatation.

The fibrin plugs that clotted in the wound also form in the lymphatic vessels.

White cells (leucocytes) enter the inflammatory field: firstly the polymorphonuclear cells (PMN), forming a barrier against infection; and later the macrophages, vital elements in the healing process, responsible for phagocytosis of necrotic tissue, neoangiogenesis (new blood vessel growth) and fibroblast stimulation.

Leucocytes, on arrival at a site of inflammation, release chemical mediators, which control subsequent accumulation and activation of other cells. Broadly, these fall into 4 enzyme systems: the complement system, the clotting system, the fibrinolytic (plasmin) system and the kinin system.

Endogenous mediators (produced by the body's immune system) are released at the site of injury by a number of cell types that either contain them as preformed molecules within storage granules, e.g. histamine, or which can rapidly synthesize them as soon as they are required.

Mononuclear phagocytes (monocytes and macrophages) are a central component of inflammation, producing many components which participate in or regulate the different plasma enzyme systems, and hence the mediators of the inflammatory response.

They are also actively phagocytic and are involved in microbial killing, as are neutrophils. (The latter are short-lived 'kamikaze' cells, whereas mononuclear phagocytes have a longer life and can also proliferate at the injury site).

Macrophages have 2 important roles in the process of repair.

Firstly, they have the job of phagocytosis: by fixing to bacteria, extending their membrane around them, then enzymatically dissolving and digesting them.

Optimal phagocytosis requires maintenance of an adequate oxygen supply, so ischaemic tissue, which has impaired oxygen supply, is at greater risk of infection.

Secondly, macrophages act as 'director cells' for repair by virtue of their influence on scar formation. They dispose of necrotic (dead) tissue in the area.

As macrophages ingest microorganisms, they excrete the products of digestion, which include ascorbic acid, hydrogen peroxide and lactic acid, as by-products of phagocytosis.

Hydrogen peroxide aids in controlling anaerobic microbial growth, whilst ascorbic acid and lactic acid are thought to signal the extent of damage, their accumulation initiating a further influx of macrophages.

Hence there may arise an intense and prolonged inflammatory response; chronically activated

macrophages cause a chronic inflammation. Steroids inhibit macrophage levels.

Macrophages may also be involved in vascular regeneration (neovascularisation), which brings oxygen and nutrients into the injured tissue.

Mast cells and basophils, together with platelets, secrete vasoactive mediators. Their function is partially under the control of cytokines.

The mast cells also release hyaluronic acid and other proteoglycans into the wound area; these bind with the watery wound fluid to create a gel.

Early phase mediators are produced by mast cells and platelets, and include chemoattractants (e.g. C5a) and cytokines such as IL-1, IL-6, and TNF-.

Later mediators are responsible for the regulation of vascular events occurring from about 6-12 hours after initiation of inflammation.

The later vascular events are mediated, at least in part, by products of arachidonic acid.

Other inflammatory mediators may be exogenous (from outside the body) such as endotoxins from bacterial infection, which can trigger complement activation, resulting in the formation of anaphylatoxins, which in turn cause vasodilatation and increase vascular permeability.

One of the acute phase reactants is fibrinogen, which coagulates in the wound and in the

surrounding tissues that are now fluid filled.

The coagulated gel later matures into a dense, binding scar. Haematomas, the result of ongoing bleeding in the wound, create more abundant exudate, which may be a stimulus to scar formation.

Serous transudate can be diminished by the classic 'RICE' regimen (rest, ice, compression, and elevation). Pharmacological use of steroids and aspirin can target transudative oedema.

The inflammatory phase ends when there is a clean wound bed ready for healing.

The macrophages 'direct' the next stage of repair by chemically influencing the number of fibroblastic repair cells activated via a growth factor, which is also produced by platelets. T

he next phase is transitional repair, during which a scar-tissue 'patch' forms. Usually, this stage begins a few days after an injury and lasts a few weeks.

However, following severe or repeated injury, or if the scar tissue is damaged, the phase may be prolonged.

This phase has also been termed the fibroplastic phase because it involves fibroblasts as the primary scar tissue producing cells.

Migratory fibroblasts follow the fibrin meshwork created earlier in the wound fluid milieu, which bathes all injured structures, thus allowing the fibroblast access to the entire wound. Once in situ, the fibroblast begins synthesis of collagen.

Fibroblasts synthesise nitric oxide, which acts as a vasodilator as well as stimulating collagen production by the fibroblasts.

Collagen production involves a highly complex biosynthetic pathway.

Each specific collagen type is encoded by a specific gene, the genes for all of the types being located on a various different chromosomes.

There are some 20 types of collagen in the body. All have a triple helix structure.

Initially, a precursor form of collagen, called procollagen, is produced.

Procollagen contains extension propeptides, which make it very soluble, and therefore easy to move within the cell as it undergoes further modifications.

As the collagen molecule is produced, it undergoes many changes, known as post-translational modifications.

One of the first modifications to take place is the very critical step of hydroxylation of selected proline and lysine amino acids in the newly synthesized procollagen protein. Specific enzymes, called hydroxylases, are responsible for these important reactions needed to form hydroxyproline and hydroxylysine.

The hydroxylase enzymes require Vitamin C and Iron as co-factors. Hence these are important factors in wound healing.

In vitamin C deficient patients, hydroxyproline may be deficient so collagen chains are unable to form in a proper helical structure and thus are weak and easily destroyed.

The trace metal manganese has also been found to be vital for a step called glycosylation, which is important in determining the chemical and structural characteristics of the newly formed collagen and may influence fibril size.

Glycosylation enzymes are more prevalent in young people, decreasing with age.

As the procollagen is secreted from the cell, it is acted upon by specialized enzymes, called procollagen proteinases, which remove both of the extension peptides from the ends of the molecule, thus rendering it much less soluble.

Parts of these digested end pieces may re-enter the cell and play a part in regulating the amount of collagen synthesis by a feed-back type of mechanism.

The processed molecule is now known as collagen and subsequently has a role in fibre formation.

In the extracellular spaces, another post-translational modification takes place as the triple helical collagen molecules line up and begin to form fibrils and then fibres.

This step is called crosslink formation and is promoted by another specialized enzyme called lysyl oxidase.

This reaction places stable cross links within (intramolecular cross links) and between the molecules (intermolecular cross links).

The crosslink formation is the critical step that gives the collagen fibres strength, which approaches that the tensile strength of steel on a per weight basis.

However, scar collagen is weaker than the original collagen, having only a maximum tensile strength of 70-80% that of the original tissue.

This is because it does not regain the original structure.

Collagen structure can be visualised by imagining the individual molecules as a piece of sewing thread.

Many of these threads, termed fibrils, are wrapped around one another to form a string. These strings then form cords; the cords associate to form a rope and the ropes interact to form cables.

The structure is just like the steel rope cables on a suspension bridge.

The final phase, maturation, tends to begin 6- 12 weeks after the injury.

During this phase, the repair process is a mixture of creation of new normal tissue and breaking down the scar-repair.

If there is a disturbance in these processes, an abnormal scar can result.



