Cell/cytokine/ Mechanical load/ Mechanical structure	Phase	Produced by	Role
Pro-Inflammatory cytokines			
INF- γ	Inflammation/ Remodeling	• Predominantly by natural killer (NK) and natural killer T (NKT) cells • T helper cells (specifically, Th1 cells), cytotoxic T cells (TC cells), macrophages, mucosal epithelial cells	• Its predominant effects include resident macrophage and neutrophil activation in order to increase cytotoxicity, and an intensification of the local inflammatory response by increasing IL-1β, NO, and TNF-α production in macrophages. • IFN-γ furthermore plays an important role in the remodeling of wound tissues; where overproduction of this factor locally can decrease wound contraction and collagen synthesis (reduces the number of myofibroblasts)
TNFa	Inflammation	• Neutrophils • Monocytes • Fibroblasts	• Chemotactic to neutrophils and macrophages • Activate macrophages • Stimulate expressions of TNF-α, IL-1β, IL-6 and IL-8 in macrophages • Mitogenic to fibroblasts (proliferation) • Stimulate expression of IL-6 in fibroblasts • Stimulate expression of MMP-8 in neutrophils
IL-1β	Inflammation	• Platelets • Macrophages • Neutrophils	• Chemotactic to neutrophils and macrophages • Activate macrophages • Stimulate expressions of TNF-α, IL-1β, IL-6 and IL-8 in macrophages • Mitogenic to fibroblasts (proliferation) • Inhibit collagen synthesis in fibroblasts
IL-6	Inflammation	• Macrophages • Fibroblasts	• Chemotactic to neutrophils • Stimulate collagen synthesis in fibroblasts

			• reduces the production of fibronectin, albumin, and transferrin • Production of neutrophils in the bone marrow. It supports the growth of B cells and is antagonistic to regulatory T cells.
IL-8	Inflammation	• Macrophages • Fibroblasts • Epithelial cells	• Inhibit collagen synthesis in fibroblasts • Chemotactic to neutrophils (but also other granulocytes, causing them to migrate toward the site of infection) • A potent promoter of angiogenesis
Anti-inflammatory cytokines			
IL-4	Inflammation	• Initial producer unknown • TH2 cells (positive feedback)	• Promotes transition of TH0 cells to TH2 cells. • IL-4 decreases the production of Th1 cells, macrophages, IFN-gamma, and dendritic cell IL-12. • The presence of IL-4 in extravascular tissues promotes alternative activation of macrophages into M2 cells and inhibits classical activation of macrophages into M1 cells. An increase in repair macrophages (M2) is coupled with secretion of IL-10 and TGF-β that result in a diminution of pathological inflammation. Release of arginase, proline, polyaminases and TGF-β by the activated M2 cell is tied with wound repair and fibrosis
IL-10	Inflammation	• Macrophages • TH2 cells	• Inhibit activation of neutrophils and macrophages • Inhibit expression of TNF-α in neutrophils, macrophages and fibroblasts • Inhibit expression of IL-1β and IFN-γ in macrophages • Inhibit expressions of IL-6 and IL-8 in macrophages and fibroblasts • Stimulate expression of TGF-β in macrophages and

			fibroblasts • Stimulate expression of IL-10 in macrophages • Inhibit activated neutrophil survival (migration and apoptosis)
Growth Factors			
PDGF	Contraction	• Released form platelets early upon activation • Macrophages • Fibroblasts	• Stimulates collagen synthesis • Attractant leukocytes (stimulates chemotaxis, proliferation, and new gene expression in monocytes-macrophages and fibroblasts)
TGFB	Contraction	• Released form platelets early upon activation • Macrophages • Fibroblasts	• Chemotactic to neutrophils, macrophages and fibroblasts • Inhibit expression of TNF-α in neutrophils, macrophages and fibroblasts • Inhibit expression of IL-1β in macrophages (minimal effect) • Activate resting fibroblasts • Stimulates resting monocytes – upregulates inflammatory response • Mitogenic to fibroblasts (proliferation) • Stimulate collagen synthesis in fibroblasts • inhibits activated macrophages • fibroblast migration, maturation and ECM synthesis
Cells			
Endothelial Cells (EC)	Inflammation/ Contraction		• Influx neutrophils, followed by monocytes/macrophages • endothelial cells control the adhesion and migration of inflammatory cells, as well as the exchange of fluid from the bloodstream into the damaged tissue (Allowing white cells to move through blood vessel)

Neutrophils (PMNs) *Resting*, *Activated*, *Apoptotic*, *Necrotic*	Immune system/ Inflammation/ Contraction	• Stem cells in the bone marrow	• Recruiting and activating other cells of the immune system • Neutrophils play a key role in the front-line defense against invading pathogens. • Neutrophils have three methods for directly attacking micro-organisms: phagocytosis (ingestion), degranulation (release of soluble anti-microbials), and generation of neutrophil extracellular traps (NETs). IFN-γ TNF-α IL-1β IL-12 IL-1Ra IL-8
Macrophages – *Activated*, *Resting*	Immune system/ Inflammation/ Contraction	• Cytokines (by neutrophils) and bacterial endotoxins • IFN-γ is the most potent macrophage-activating factor • Some cytokines can upregulate the production of cytokines by macrophages (IL-3, IFN gamma) while others can inhibit it (IL-4, IL-10, TGF beta).	• Infiltrate after injury in order to clean the wound of bacteria, foreign debris and dead cells. • As the tissue begins to repair, the overall macrophage population transitions to one that promotes anti-inflammatory effects (traditionally and collectively referred to as “M2” macrophages), and the migration and proliferation of fibroblasts, keratinocytes and endothelial cells to restore the dermis, epidermis and vasculature, respectively. • Activated macrophages also release proteases, neutrophil chemotatic factors; reactive oxygen species such as nitric oxide and superoxide; cytokines such as tumor necrosis factor-alpha (TNF-alpha), interleukin one and eight (IL-1 and IL-8), eicosanoids, as well as growth factors. • synthesize and release a large variety of cytokines (IL-1, IL-1ra, IL-6, IL-8, IL-10, IL-12, TNF alpha, IFN gamma, TGF beta)

Fibroblasts	Contraction	• Summoned to the wound site via chemoattractants, such as platelet-derived growth factor (PDGF), interleukin-1 beta (IL-1β) and tumour necrosis factor-alpha (TNF-α). migrate into the wound bed via a mechanism called 'contact guidance' • The fibroblasts migrate along the fibrin-fibronectin plug into the wound site • With the subtle difference that the fibroblasts move according to the gradient of TGF-β. • The migration of the fibroblasts is also influenced by the orientation of the collagen (This complex ECM matrix supports and regulates the migration and activity of the fibroblasts)	• Involved in key processes such as breaking down the fibrin clot, creating new extra cellular matrix (ECM) and collagen structures to support the other cells associated with effective wound healing, as well as contracting the wound. • In the presence of transforming growth factor-β, fibroblasts undergo a phenotypical differentiation, whereby the structure and function are altered. stimulate fibroblasts to attach, via integrin containing adhesions, to fibrous proteins in the ECM. This binding causes them to begin to express stress fibres (collagen): At the end of the inflammatory phase and beginning of the proliferative phase (24–48 hours post injury), the first fibroblasts appear at the site of injury. Fibroblasts infiltrate and degrade the fibrin clot by producing various matrix metalloproteinases (MMPs), replacing it with extracellular matrix (ECM) components (collagen) • When arrived at wound iste: They begin to proliferate and produce MMPs and other proteinases, such as seperinase, to remove denatured proteins and provisional matrix-associated material not required in the healed wound. These proteinases are tightly controlled by tissue inhibitors of metalloproteinases (TIMPS), which are also produced by fibroblasts. 9 Simultaneously, they also produce new ECM, initially relatively rich in collagen III, fibronectin and hyaluronic acid

			The fibroblasts and leukocytes will lose activity as time proceeds.
Myofibroblasts	Contraction	• Myofibroblasts are characterised by the expression of α-smooth muscle actin (α-SMA), which gives them increased contractile power, as well as cell–matrix and cell–cell adherins, which is in stark contrast to those fibroblasts found in uninjured ECM • The exact origin of the myofibroblasts seen in the healing wound is not clear. The majority are recruited locally from the dermis and tissues around the wound site • Myofibroblasts have also been shown to express integrin (αvβ3), which allows them to adhere to and migrate on fibrin	• Myofibroblasts are responsible for wound closure that occurs in healed acute wounds • Myofibroblasts possess bundles of microfilaments which terminate at the cell surface in a specialized adhesion complex, termed the fibronexus or mature local adhesion. This complex bridge the myofibroblast's internal microfilaments with extracellular fibronectin domains thus functioning as a contractile mechanism that enables these cells to generate force to the surrounding extracellular matrix. This contractile force is maintained over time and reinforced by the deposition of collagen • Are a consequence of the shortening of the collagen strings by the myofibroblasts?
Alkaline Phosphatase **(AP)**	Immune system	• Alkaline Phosphatases are a group of enzymes found primarily the liver (isoenzyme ALP-1) and bone (isoenzyme ALP-2). There are also small amounts produced by cells lining the intestines (isoenzyme ALP-3), the placenta, and the kidney (in the proximal convoluted tubules).	• reduce inflammation by dephosphorylating inflammation triggering moieties like bacterial lipopolysaccharides (LPS) and extracellular nucleotides
Fibers			
Collagen	Contraction	• Fibroblasts • Since it is known that diffusion in the fibrin is slower than in the collagen network	• Collagen repairs tissue damage • Collagen fragments are chemotactic to neutrophils and macrophages

Fibrin/Fibronectin	Contraction	•	• Migration Fibroblasts and Macrophages • This fibrin-fibronectin plug is also the main structural support for the wound until collagen is deposited
Elastin	Contraction	• Fibroblasts	• Together with Collagen in new ECM