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| ***Alkaline Phospatase and it’s role in the Immune System - Sloot*** | **A multi-agent cell-based model for wound contraction - Boon** | **Computational Modeling of Inflammation and Wound Healing - Ziraldo** |
| Inflammation Triggering Moeties **(ITMs)** |  | "Endotoxin" is produced by simulated infectious vectors  (activates ECs, PMNs and Monos)  Cytotoxin (  1. It reduces "infection" by "cytotox." This is the bactericidal effect.  2. It reduces "oxy" by "cytotox." This is the cytotoxic effect on otherwise undamaged ECs) |
| Alkaline Phosphatase **(AP) –** *Endogenous in liver, supplemented,* |  |  |
|  |  | GCSF (  1. stimulates the bone marrow to produce granulocytes and stem cells and release them into the bloodstream  2. Inflammatory mediators such as interleukin (IL)-1, tumor necrosis factor-α (TNF), and toll-like receptor (TLR) ligands including microbial components such as lipopolysaccharide (LPS) and endogenous molecules such as the acute-phase protein serum amyloid A (12) have been shown to induce G-CSF production)  PAF (is a potent phospholipid activator and mediator of many leukocyte functions, platelet aggregation and degranulation, inflammation, and anaphylaxis  **produced by activated ECs**)  sTNFr (cytokine receptor) |
| Pro-inflammatory Cytokines | tPA  PDGF  TGFB | TNFa (**produced by both PMNs and Monos**)  IL-8 (**produced by macrophages/Monos and EC and is chemotactic for PMNs**)  IL-12 (**produced by TH1 cells**)  IL-1 (**produced by both PMNs and Monos**)  IL-6  IL- (is an important activator of macrophages and inducer of Class II major histocompatibility complex (MHC) molecule expression) |
| Anti-inflammatory Cytokines |  | IL-4 (**produced by TH2 cells (positive feedback) and promotes transition of TH0 cells to TH2 cells. Initial IL-4 producer unknown**)  IL-10 (**produced by Monos and TH2 cells**)  IL-1ra |
| Neutrophils – *Resting, Activated, Apoptotic, Necrotic* | Neutrophils | Neutrophils |
| Macrophages – *Activated, Resting* | Leukocytes | Macrophages |
|  | Fibres -  Collagen  Fibrin |  |
|  | Fibroblasts  Myofibroblasts | Fibroblasts |

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| Cell/cytokine/  Mechanical load/  Mechanical structure | Phase | Produced by | Role |
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| **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 | * 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 |
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| **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) |
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| **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 |
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| **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 |  | PMNs are mobile agents |
| Endotoxin | inflammation | infectious vectors | activates ECs, PMNs and Monos.   In monocytes and macrophages, three types of events are triggered during their interaction with LPS:   1. Production of cytokines, including IL-1, IL-6, IL-8, tumor necrosis factor (TNF) and platelet-activating factor 2. affect neutrophil chemotaxis and accumulation. The result is inflammation. 3. Activation of the coagulation cascade |
| Cytotoxin | inflammation |  | 1. It reduces "infection" by "cytotox." This is the bactericidal effect.  2. It reduces "oxy" by "cytotox." This is the cytotoxic effect on otherwise undamaged ECs) |
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| Alkaline Phosphatase **(AP)** | Immune system |  |  |
| Macrophages – *Activated, Resting* | Immune system/ inflammation | cytokines and bacterial endotoxins  IFN-γ is the most potent macrophage-activating factor | 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. These products of activated macrophages result in the tissue destruction which is a hallmark of inflammation |
| TH0-cells | Inflammation | [10.1371/journal.pone.0179015](https://dx.doi.org/10.1371%2Fjournal.pone.0179015) | represent progenitor cells for the two cell types above |
| TH1 cells represent the pro-inflammatory T-cells; they are Blue. | Inflammation | are activated in the presence of "IL-12."  mainly develop following infections by intracellular bacteria and some viruses | produce interferon-gamma, interleukin (IL)-2, and tumour necrosis factor (TNF)-beta, which activate macrophages and are responsible for cell-mediated immunity and phagocyte-dependent protective responses |
| TH2 cells represent anti-inflammatory T-cells | Inflammation | are activated in the presence of "IL-10.  predominate in response to infestations by gastrointestinal nematodes | type 2 Th (Th2) cells produce IL-4, IL-5, IL-10, and IL-13, which are responsible for strong antibody production, eosinophil activation, and inhibition of several macrophage functions, thus providing phagocyte-independent protective responses. |
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| tPA | Contraction | Which is released by the endothelial cells | This cytokine breaks down the clot and  hence it decays the fibrin |
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| Collagen | Contraction | Since it is known that diffusion in the fibrin is slower than in the collagen network | The sourcing term Tβ represents the secretion by the leukocytes,in  the presence of collagen and fibrin networks  is a critical cell movement regulator. Further, we take into account that the tissue in the upper part of the dermis  (the papillary dermis) contains loosely collagen fibers   * Collagen repairs tissue damage * Collagen fragments are chemotactic to neutrophils and macrophages |
| Leukocytes | Contraction |  |  |
| Fibrin | Contraction |  |  |
| Fibroblasts | Contraction | The equation of migration of fibroblasts is analogous to the relation of migration of leukocytes  with the subtle difference that the fibroblasts move according to the gradient of TGF-β.  That the survival rate is not determined by any of the  Concentrations TGF-β, PDGF or tPA,  The migration of the fibroblasts is influenced by the orientation  of the collagen | This implies that the fibroblasts and leukocytes will lose  Activity as time proceeds.  The fibroblasts migrate along the fibrin-fibronectin  plug into the wound site where they synthesise collagen and elastin and begin remaking the  extracellular matrix (ECM) |
| Myofibroblasts | Contraction | Thus, the α-smooth muscle actin–expressing fibroblast, known as the myofibroblast, | 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 bridges 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  The plastic forces  Are a consequence of the shortening of the collagen strings by the myofibroblasts. |
| GCSF | inflammation | Inflammatory mediators such as interleukin (IL)-1, tumor necrosis factor-α (TNF) have been shown to induce G-CSF production  Monos | stimulates the bone marrow to produce granulocytes and stem cells and release them into the bloodstream |
| PAF | inflammation | activated ECs | is a potent phospholipid activator and mediator of many leukocyte functions, platelet aggregation and degranulation, inflammation, and anaphylaxis  chemotaxis for PMNs and Monos |
| sTNFr | inflammation | ? | TNFα antagonists |
| IL-12 | inflammation | TH1 cells | transition of TH0 to TH1 cells |
| IL-1RA | Inflammation |  | IL-1ra levels tend to increase later than IL-1 levels, suggesting that IL-1ra functions to block further IL-1 activity and has a role in the termination of the inflammatory response.  preventing IL-1 from sending a signal to that cell. |
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