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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  IFNγ (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/etc... | phase | Produced by | role |
| INF-g | inflammation | commonly expressed in Escherichia coli, however, the resulting product of the prokaryotic expression system is not glycosylated with a short half-life in the bloodstream after injection | IFNγ is an important activator of macrophages and inducer of Class II major histocompatibility complex (MHC) molecule expression |
| 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 |
| TNFa | inflammation | PMNs and Monos | PMN activation, adhesion, migration and apoptosis   * 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-8 | inflammation | macrophages/Monos and EC | chemotactic for PMNs   * Chemotactic to neutrophils * Inhibit collagen synthesis in fibroblasts |
| IL-12 | inflammation | TH1 cells | transition of TH0 to TH1 cells |
| IL-1 | inflammation | PMNs and Monos | possess strongly proinflammatory effect  "IL-1" is incorporated into the calculations for "IL-8," "IL-10," "IL-12," "GCSF," and "INF-g.  PMN adhesion |
| IL-6 | inflammation | macrophages | inhibitory effects on TNF-alpha and IL-1, and activation of IL-1ra and IL-10.  responsible for stimulating acute phase protein synthesis, as well as the production of neutrophils in the bone marrow. It supports the growth of B cells and is antagonistic to regulatory T cells.   * Chemotactic to neutrophils * Stimulate collagen synthesis in fibroblasts |
| IL-4 | inflammation | TH2 cells (positive feedback)  **Initial IL-4 producer unknown** | promotes transition of TH0 cells to TH2 cells.) |
| IL-10 | inflammation | Monos and TH2 cells | PMN migration and apoptosis, activation status of Monos, and the transition of TH0 to TH2 cells   * Inhibit expression of TNF-α in neutrophils, macrophages and fibroblasts * Inhibit expression of IL-1β 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 * Inhibit activation of neutrophils and macrophages |
| 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. |
| 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) |
| Endothelial Cells (EC) | Inflammation/ contraction | activated by Endotoxin >= 1 or oxy < 60 | Allowing white cells to move through blood vessel. |
| Neutrophils (PMNs)  *Resting, Activated, Apoptotic, Necrotic* | Immune system/ inflammation/ contraction | "PAF," "endotoxin" and "IL-8" as the PMN chemotactic factors | PMNs are mobile agents |
| 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. |
| TGFB | Contraction | secreted by many cell types, including macrophages (leukocytes),   * **Activation by protease and metalloprotease**   Plasmin and a number of Matrix metalloproteinases (MMP) play a key role in promoting tumor invasion and tissue remodeling by inducing proteolysis of several ECM components.   * **Activation by pH** * **Activation reactive oxygen species (ROS)** * **Activation by thrombospondin-1** | Attracts macrophages and fibroblasts  Stimulates resting monocytes – upregulates inflammatory response  While also ***downregulating*** cytokine production in monocytes and macrophages  inhibits activated macrophages   * Chemotactic to neutrophils, macrophages and fibroblasts * Inhibit expression of TNF-α in neutrophils, macrophages and fibroblasts * Inhibit expression of MMP-8 in neutrophils * Inhibit expression of IL-1β in macrophages (minimal effect) * Activate resting fibroblasts * Mitogenic to fibroblasts (proliferation) * Stimulate collagen synthesis in fibroblasts * Stimulate elastin synthesis in fibroblasts * Stimulate hyaluronan synthesis in fibroblasts |
| tPA | Contraction | Which is released by the endothelial cells | This cytokine breaks down the clot and  hence it decays the fibrin |
| PDGF | Contraction | platelets upon activation, it is also produced by other cells including smooth muscle cells, activated macrophages, and endothelial cells | Attractant leukocytes |
| 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. |
|  | Contraction |  |  |