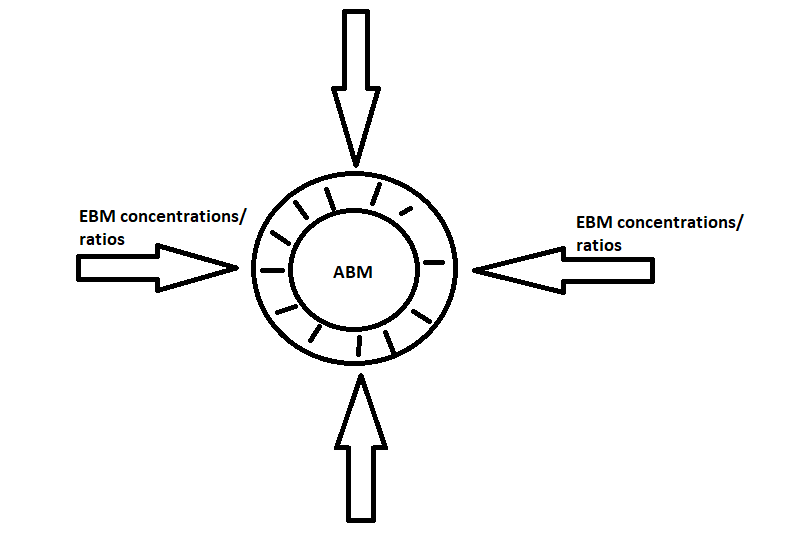
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| ***Alkaline Phospatase and it’s role in the Immune System - Sloot*** | **A multi-agent cell-based model for wound contraction - Boon** | **Computational Modeling of Inflammation and Wound Healing - Ziraldo** |
| Inflammation Triggering Moeties **(ITMs)** |  | "Endotoxin"  Cytotoxin |
| Alkaline Phosphatase **(AP) –** *Endogenous in liver, supplemented,* |  |  |
|  |  | GCSF  PAF  sTNFr |
| Pro-inflammatory Cytokines | tPA  PDGF  TGFB | TNFa  IL-8  IL-12  IL-1  IL-6  IL- |
| Anti-inflammatory Cytokines |  | IL-4  IL-10  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 * 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 |
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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 | * 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 |
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| **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 |

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| **EXTRA** |  |  |  |
| tPA | Contraction | Which is released by the endothelial cells | This cytokine breaks down the clot and  hence it decays the fibrin |
| 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. |
| 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 | d | 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.   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) |

IDEA:



– There are no frameworks that support coupling of heterogeneous models

between equation-based modeling and agent-based modeling paradigm.

EBM only uses IL-6 and IL-10. Hope we can implement the ratios of other cytokines.

Polynomial regression or something?

An Agent-Based Model of Inflammation and Fibrosis Following Particulate Exposure in the Lung