**Tissue damage Submodel**

**The model equations and parameters can be adopted from following article.**

**Article 1:** Ceresa-Coupled immunological and biomechanical model of emphysema progression-Frontiers in physiology

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**Model 1:**

* Start from an immune model where tissue is not completely destroyed (faster T recruitment or faster T kill)
* When CD8+ T cell kills an infected cell that will become the source point for secretion of anti-inflammatory cytokine (equation 8)
* Anti-inflammatory cytokine will diffuse
* Recruitment of fibroblast depends on the concentration of anti-inflammatory cytokine (equation 10)
* Fibroblast chemotaxis towards the source of maximum secretion source of anti-inflammatory cytokines
* Fibroblast deposit collagen in the damages site (equation 11)

**Model 2:**

* When viral load become 0 after infection, portion of active macrophage converts to M2 macrophage (equation 4)
* M2 macrophage move towards damage site (no cell)
* In the damage site M2 macrophage secrete anti-inflammatory cytokines
* Anti-inflammatory cytokine will diffuse
* Recruitment of fibroblast depends on the concentration of anti-inflammatory cytokine (equation 10)
* Fibroblast chemotaxis towards the source of maximum secretion source of anti-inflammatory cytokines
* Fibroblast deposit collagen in the damages site (equation 11)

**Model 3:**

* Infected cells secrete IL-10
* IL-10 converts inactive macrophage to M2 macrophage
* Portion of active macrophage converts to M2 macrophage
* M2 macrophage move towards damage site (no cell)
* In the damage site M2 macrophage secrete anti-inflammatory cytokines
* Anti-inflammatory cytokine will diffuse
* Recruitment of fibroblast depends on the concentration of anti-inflammatory cytokine (equation 10)
* Fibroblast chemotaxis towards the source of maximum secretion source of anti-inflammatory cytokines
* Fibroblast deposit collagen in the damages site (equation 11)

Finally include uptake of anti-inflammatory cytokine and when fibroblast reach to a maximum source turning the source off (for model 1)

**Article 2:** Jin-Combining experimental and mathematical modeling to reveal mechanisms of macrophage-dependent left ventricular remodeling-BMC systems biology

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**Figure:** Macrophage migration rate M(Tβ), fibroblast growth rate Fg(Tβ), and fibroblast secretion rate Fc(Tβ) plotted as functions of TGFβconcentration.

Assuming baseline = 0, followings are the function for macrophage migration, fibroblast recruitment and secretion.

**is the input signal from damaged site**

**Table: List of parameters**

|  |  |  |
| --- | --- | --- |
| **Symbol** | **Biological meaning** | **Value** |
|  | Macrophage removal rate | 0.6 day-1 |
|  | Fibroblast growth rate | 0.924 day-1 |
|  | Fibroblast apoptosis rate | 0.12 day-1 |
|  | Macrophage TGF-β production rate | 0.07 pg/cell/day |
|  | Fibroblast TGF-β production rate | 0.004 pg/cell/day |
|  | TGF-β degradation rate | 15 day-1 |
|  | Fibroblast collagen production rate | 20 μg/cell/day |

**Simulated result for μL/day**

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**Possible parameters:**

* Anti-inflammatory cytokine
* Diffusion coefficient
* Cytokine decay rate locally:
* Cytokine release rate from macrophages:
* Cytokine uptake rate by fibroblast:
* M2 Macrophages
* Cell migration rate along CI chemokine gradient: with bias 91% (0.91)
* Cell decay rate: Default (use PhysiCell built-in apoptosis model)
* Cell recruitment rate into tissue by pro-inflammatory cytokine:
* Fibroblast
* Cell migration rate along damaged tissue life in voxel: 1?
* Cell decay rate: Default (use PhysiCell built-in apoptosis model)
* Cell recruitment rate into tissue by anti-inflammatory cytokine: 20 cells/min (assumption)?

**References**

1. Trepat, X., Chen, Z., & Jacobson, K. (2012). Cell migration. *Comprehensive Physiology*, *2*(4), 2369-2392.