

1. Introduction

Peritoneal adhesions are pathological fibrotic connections forming between organ surfaces. They typically follow a surgical procedure of the thorax, abdomen or pelvis, or result from inflammatory diseases such as Crohn's or endometriosis. Adhesions can cause small bowel obstruction, chronic pain or infertility.

During the process of tissue repair after insult, a fibrin exudate is formed [1,2]. Mesothelial cells (MC) ensure the fibrin breakdown by secreting enzymes such as tissue plasminogen activator (tPA). However, adhesion promoting factors such as hypoxia or necrosis impair the fibrinolytic activity of the protective lining. Fibroblasts (FB) stemming from migration or MC phenotype transition build extracellular matrix and collagen to form long-lasting adhesions [2]. So far, there is no model available to study adhesion formation despite the lack of answer to this clinical problem.

2. Materials and Methods

We propose here a model of adhesion formation representing in 2D the volume \mathcal{B} between the peritoneal serosa $\partial\mathcal{B}_p$ and the tissue boundary $\partial\mathcal{B}_t$, where the following mechanisms occur: (i) the formation of the fibrin exudate upon tissue insult, and (ii) FB-mediated fibrosis. To this end, we implemented in Comsol Multiphysics 5.4 a system of differential equations depicting the time- and space- dependent evolution of four variables: the fibrin, collagen and tPA levels and FB concentration.

Fibrin (F_n), tPA (t_{PA}) and FB (b) evolutions are represented by an interdependent system of partial differential equations accounting from fibrin-mediated chemotaxis of FB (sensitivity χ), which evolve as follows in the volume \mathcal{B} :

$$\frac{\partial}{\partial t} \begin{bmatrix} b \\ F_n \\ t_{PA} \end{bmatrix} = \nabla \cdot \begin{bmatrix} \mu_{Fb} \nabla b - \chi b \nabla F_n \\ D^{F_n} \nabla F_n \\ D^{t_{PA}} \nabla t_{PA} \end{bmatrix} - \mathbf{d} \cdot \begin{bmatrix} b \\ F_n \\ t_{PA} \end{bmatrix}, \quad (1)$$

where $\mathbf{d} = [a_b, d_{F_n}, d_{t_{PA}}]$ accounts for FB apoptosis \mathcal{A}_b , fibrin (d_{F_n}) and tPA degradation ($d_{t_{PA}}$). The time-derivative of the collagen content c is defined as a linear function of FB activity and collagen degradation.

Constant fibrin ϕ_{F_n} and FB ϕ_b fluxes are imposed on the injury site. Outside the injury, a fibrinolytic tPA flux $\phi_{t_{PA}}$ is set to a constant flux $\phi_{t_{PA}}^0$ to account for the action of MCs and decreased to $\phi_{t_{PA}} = \phi_{t_{PA}}^0 / 100$ for an adhesive (pathological) repair.

3. Results

Figure 1 highlights FB seeding into the fibrin exudate, producing collagen, therefore connecting the tissue and serosa boundaries. The black and white lines mark the bounds of the collagen-rich volumes in adhesive and healthy repairs, respectively (threshold $c \geq 100$ $\mu\text{g}/\text{mg}$, representing dense adhesions as per histological data [2]). In the case of a healthy regeneration, the inhibition of fibrin by tPA-mediated fibrinolysis prevents formation of the dense connective tissue bond (white line).

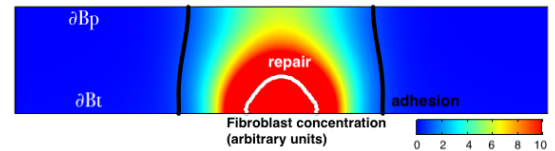


Figure 1: Fibroblast concentration 10 days after tissue trauma, resulting in an adhesive bond (black) or repair (white) depending on fibrinolytic activity.

4. Discussion and Conclusions

This is the first attempt to quantify the mechanisms of adhesion formation. We successfully depicted the main events following tissue trauma. Future work will investigate the next remodelling steps, in particular involving innervation and *in vivo* mechanical stimulation.

5. References

1. Brochhausen et al., J Gastrointest Surg; 16(6):1256-1274 (2012).
2. Binnebösel M et al., Langenbecks Arch Surg; 393:59–66 (2008).