Defects in resolution of inflammation

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The acute immune response is a vital function in virtually all living organisms. In humans, a key mechanism is the generation of vast numbers of *neutrophils*—small, motile white blood cells (*leukocytes*)which locate target material (a bacterial invasion or harmful somatic elements) and remove it via *phagocytosis*. The inflamed state, however, has the potential to damage the surrounding tissue: after a short time neutrophils undergo *apoptosis* and soon after enter *necrosis*. Necrotic cells may leak their cytotoxic and autoimmunogenic contents such as myeloperoxidase and double-stranded DNA. Many authors refer to the 'paradox of inflammation', highlighting the fine balance which must be achieved between too much and too little neutrophil response.

Macrophages are much larger, specialised cleaner cells which respond to signalling proteins on the surface of apoptotic neutrophils and remove them from tissue before they become necrotic. This process, often termed *efferocytosis* (effero = 'to bury the dead') is essential in maintaining healthy tissue and an estimated 10^{11} neutrophils are cleared in a healthy individual each day. Apoptotic cell counts in blood samples from healthy individuals are negligible. In a number of chronic inflammatory diseases, however, apoptotic cell counts are raised, suggesting a link between chronic inflammatory conditions such as cystic fibrosis, bronchiectasis and chronic obstructive pulmonary disease (COPD) and reduced function of efferocytosis. This defect is also of interest in cancer research since the cell-growth and proliferation signals coupled with repeated damage and repair of tissues provides an environment in which tumours may more easily propagate.

Interesting research topics include determining which receptor systems and signalling pathways are most important in efferocytosis and how these change between a homeostatic and a pro-resolution state; whether huge numbers of neutrophils 'exhaust' the macrophages, leading to decreased function; what the post-resolution fate of local macrophages is and how drugs might enhance or inhibit clearance of apoptotic cells.

Project proposal

I propose to construct an *agent-based model* (ABM) of local, alveolar neutrophils and macrophages in order to determine which parameters are most important in controlling efficient clearance of apoptotic neutrophils. Since a huge number of receptors and signalling molecules are potentially involved in this process, the model should be as simple as possible; representing the pathways indicated as most important and also best documented in the literature. Frequently cited cell-receptors in the resources listed below include CD91, Mer and SR2 and leukocyte behaviour is modulated by pro- and anti-inflammatory proteins. Chief among these are TNF-α, IL-8 and IL-6 (pro); and TGF-β, VEGF, IL-10 and HGF (anti). In early versions of the model, this system may be simplified to a single pro-inflammatory and a single anti-inflammatory signalling molecule.

Ongoing consultation with experimental teams in the life-sciences will consolidate and clarify the data on which behaviour in the model will be based.

Spatiotemporal structure

We are seeking to model the resolution phase of the inflammatory response; that is, the initial target (bacteria or other harmful elements) has been removed and the population of neutrophils is about to begin undergoing apoptosis. The populations of neutrophils and macrophages will be made up of individual agents and their interaction will depend on their spatial position. These interactions will determine the individual behaviours of the agents.

Deliberately omitted components will be: any kind of extracellular matrix, for example a tissue structure or vasculature; clearance of apoptotic neutrophils by cells other than macrophages (eg. dendritic cells) and circulating populations of systemic (as opposed to local) leukocytes.

Details as-yet undetermined are:

- Whether the agents will move by *chemotaxis* (up chemical gradients) or randomly
- Whether the environment is two- or three-dimensional
- The lifespan of the macrophages
- Whether to include a volume change to illustrate 'physical' inflammation

Procedure

A proposed workflow for the project is:

1. Conceptualise biological system, assign entities
2. Define behaviours based on known mechanisms in literature/online resources
3. Formulate hypotheses for gaps in knowledge
4. Formalise conceptual model (implement: Java & MASON[1])
5. Run model

[1]Multiagent simulation toolkit: http://cs.gmu.edu/~eclab/projects/mason/

6. Compare results with data/literature
7. Reformulate model
8. Re-test ...

Evaluation

Agent-based modelling is a powerful and illustrative tool for modelling biological systems. It is simpler to model complex, multi-scale systems using this approach than with an analytical model. It is also easier to build in intuitive visualisation of the system under study, making the dialogue between modeller and experimentalist more fluent.

It also has disadvantages in that it can be harder to define the range of possible outcomes in an unconstrained system; causation can be hard to identify in systems with large numbers of components and models with biologically realistic numbers of agents may be highly computationally intensive.

For this reason, this project will seek to assess the suitability of an ABM approach in addressing problems of this kind as well as investigating the biological problem itself.

Resources

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