

SYSBIOMED Workshop:
Systems Biology and Inflammatory Diseases (IDs)
 September 7th, 2007, Frankfurt am Main, Germany

Participants

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Discussion

The half-day workshop consisted of a thorough discussion of the options systems biology (SB) approaches could provide to research on inflammatory processes. The participants believe that the timing is quite right for starting SB projects in medical research since technology, tools and components required for quantitative measurements in biological systems are currently emerging. Depending on the specific question, appropriate methods should allow for reasonable conclusions. In order to elucidate central mechanisms of the immune system across all levels one has to identify key players responsible for IDs, relying on data from *in vivo* models (knockout mice) as well as dish cultures.

Primary immune cells are considered "good models" due to the high standard of available cell culture technologies and the access to *in vivo* models, i.e. KO mice.

The following disease-relevant functions of certain cell types were discussed with respect to the amenability for SB approaches:

- T-cell activation
- T-cell survival/ renewal
- T-cell memory
- macrophage activation
- neutrophil functions

Given the high technological standards of current cell biotechnology T-cells appear as the preferred target system while neutrophils which are involved in host defence were regarded as less suitable for SB projects due to technical reasons, i.a. the limited range of functions and the comparably difficult cultivation *in vitro*.

The participants agreed on research priorities ('big questions') in the ID arena which would benefit most from SB:

1 *T cell control/ activation*

Elucidate the *decision process* governing cell death and growth, i.a. cell-cycle dependent mechanisms, project would be linking different communication processes involved (external signals, CC). Dynamic gene expression data and proteome information could be provided at high resolution. The factors governing the activation are still not completely identified.

2 *Chronic inflammation*

apparently is the underlying cause of severe disorders, including the runaway proliferation of mammalian cells. Roughly 15% of human deaths from cancer are associated with chronic viral or bacterial infections. Various disease-related models are accessible, especially when looking at T cell renewal. The long-term regulation of T cells is not well understood: what makes them replicate fast, then remain almost silent? What is the role of the cells of the micro-environment?

3 *Key players: COX1/COX2 dependent messengers*

Shedding light into the mechanisms triggered by non-steroidal messenger molecules is highly desirable with regard to recent failures in the drug market (Vioxx). SB could help to find very general principles underlying many phenomena, e.g. angiogenesis. Novel insights and sound knowledge could help to alleviate FDA-inspired tight regulations of COX inhibitors.

4 *Key players: NF- κ B*

Signalling pathways via nuclear factor- κ B (NF- κ B) are central to many cellular processes with pathologic relevance. Since the signalling networks vary between different cell types SB research would deliver insights gained from comparing primary and other cells.

5 *Immunosuppression*

What are the mechanisms behind the turning-off of the immune systems in certain, often chronic disease conditions? How do cancer cells induce apoptosis? Which cells are affected? Modelling approaches applied to established model systems are expected to provide deeper insights.

6 *Gene transcription*

There are still no good models explaining the rates of gene transcription (exception: the *lac*-operon modeled on the basis of the known repressor proteins). Elucidating the role of key genes and the hierarchy of genetic organisation is possible by combining advanced research on gene activities and modelling approaches. Decision processes in the development of T helper cells (T_{H1} vs. T_{H2}) is an example from the ID area that could be investigated.

7 *Interaction of antigen presenting cells (APCs) and effector cells*

Current efforts to model this important processes are static, only a few players are known.

8 Interaction of ceratinocytes and fibroblasts

This systems constitutes a good model, data are accessible.

9 Proliferation vs. cell death

The dynamics of immune cell populations should be well amenable to modelling approaches since clean data are available at different levels. Questions to be addressed: why does proliferation stop? What is the effect of 'noise', i.e. the robustness of the systems' response to stochastic changes?

Challenges and Obstacles

Data:

Data from assays measuring cytokine profiles are needed, the respective technologies are being currently developed. Quantitative dynamic expression data are hard to obtain, respective technologies (e.g. advanced multiphoton microscopy) are under development. Single cell experiments are considered a valuable source of data. Careful pre-processing of data is considered key to the efficient collaboration of laboratories. Such work requiring sufficient technical staff is usually underestimated in proposals.

Models:

On the theoretical side proper approximation algorithms are indispensable as are tools that allow the interpretation of dynamic imaging data carrying information on gene activities. There is a need for modelling as the current knowledge is low: although 50% of the data of signalling pathways via IL-2 is available, the situation concerning other pathways is far worse (20%). There is good dynamic data on NF- κ B pathways. Modelling is expected to help identify the missing components and factors. Modelling is expected to shed light into the secrets of the immune system as listed above.

On research programmes

The *raison d'être* of SB essentially is the added value to science from the productive, complementing interaction of molecular biologists and modellers. On attacking 'Big Questions' (e.g. How are T cells turned off?) a set of relevant sub-areas has to be defined and teams with complementing expertise must join their forces.

Generally, the duration of SB projects is considered too short. Longer projects with more flexibility would be recommended. People with sound experience are in short supply, SB research projects shall serve to provide training opportunities to young talented scientists. Medical researchers are interested in participating in SB projects, clinicians, however, still stay distant.

Scale issues arising from the type of a research programme needed to answer a question, e.g. the large numbers of people and money systematic knock-in studies would require, were briefly addressed. Future programmes should increase budgets for video-conferences and go with less bureaucracy. On the European level SYBILLA, systems biology of T-cell activation in health and disease, started in April 2008. It is a European Union-funded large integrated project in framework program 7 (FP7). The goal of SYBILLA is to understand the intracellular signalling network of T cells that determines T cell fate.