A DYNAMIC THEORY OF SELF / NON-SELF DISCRIMINATION

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June 23, 2014
Complex systems require a vision

Complex systems need to be analyzed

- bottom-up, from their constitutive elements and links
- as a whole, under various angles

All aspects have to be reconciled into a workable mental representation = a vision
Picture of the yeast network
INTRODUCTION

The vision from which I start

- Hyper-complexity
  Elements and links
  Physical objects and virtual rules
  Control theory

- Quality-control of multiple errors
  All biological processes make mistakes
- Specificity

  Not key and lock when two macromolecules are involved

  Combination of poorly specific steps

  Largely related to space and time

  Generation of waste

- Robustness

  Ability to work decently in spite of mostly random internal dysfunctions

  external hazards
- Individual (stochastic) variations of gene expression in single cells,

- The logics of : Approximately Probably Correct (Leslie Valiant)
I - Approaching a definition of the self

- Which physical and functional borders? *Microbiota*

- Which time frame? *From infancy to aging*

Self = the physiological organism at any stage of its life

Physiology appropriately refers to medicine to normality
What self / non-self discrimination in general cannot be

It cannot be devoid

- of complexity (it cannot be simple)
- of errors
- of quality control mechanisms to make it robust
- of waste
What self / non-self discrimination of an element cannot be

It cannot be described as a digital event (0 or 1)

The immunogenicity of any element (molecule), be it self or non self, must be evaluated as a function of its concentration.

   biological reactions described by bell shape curves

   cross-reactions
MHC provides an identity, but MHC does not define the self

Adaptative immune reactions are robust, and may be seen as remarkably homogeneous (vaccination), in spite of MHC polymorphism.

Self = elements + rules
The peptidic self model: a hypothesis on the molecular nature of the immunological self.
Kourilsky P, Claverie JM.

Abstract

We propose that peptide presentation by class I and class II antigens of the major histocompatibility complex is a general phenomenon. Peptides derived from the breakdown of most or all cellular proteins and able to associate with class I or class II antigens would be continuously presented at the surface of cells. The set of peptides exposed at the surface of somatic cells, called in short the "somatic self", would be under permanent immune surveillance. A protein would be recognized as "foreign" primarily because at least one of its presented peptides does not belong to the somatic self. We speculate that the same peptide presentation process operates within cells of the immune system, and we discuss some of the possible implications. Since this "peptidic self" model imposes strong constraints on primary structures, we have undertaken a preliminary analysis of several peptides with known immunological properties. We show that they all contain patterns of amino acids not found in the protein sequence data banks available at present for the relevant organisms, in agreement with the starting hypothesis.
Peptidic self vs avidity windows

Rules more important than elements: polymorphism is permitted, which also allows for selection of many variants.
Previous and current theories of self / non-self discrimination

- Clonal deletion
- P. Matzinger Danger theory
- T. Pradeu and E. Vivier Discontinuity theory
- Z. Grossman and W. Paul
II- Hypothesis: All cells are « intelligent »

« Intelligence » is a property of certain biological complex systems, which have the potential of autonomously adopting one of many different (pseudo-) stable states.

It might be framed by the logics of « probably approximately correct » (Leslie Valiant), which involves a simple type of reiterated education towards a certain objective. This requires some type of memory.
« Intelligent » cells are constrained

- by their genetic program (apoptosis)
- by other cells
- particularly by their contacts with other cells
Cells are not equally « intelligent »

- Cells embedded in tissues are under quasi-permanent control by their neighbors.

- There are cells (not strictly embedded in tissues) which live in a certain isolation, particularly circulating cells.

- Such cells have more freedom to explore a large variety of states. In this respect, they are more « intelligent ».

- At the same time, they may drift away from their (optimum) function unless properly reset (tickled) at regular intervals
T lymphocytes are « intelligent » cells.

The above scheme applies to T lymphocytes selected in the thymus, and further selected and maintained in the periphery.

T cells self-adapt their affinity/avidity window, as proposed by Grossmann and Paul.

T cells with different, often mediocre, affinities end up with decent and rather homogeneous reactivities. This T cell « avidity maturation » is a remote equivalent of antibody affinity maturation.
Innate cells, alike macrophages, are « intelligent » too.

Polarization of macrophages is a manifestation of « intelligence ».

The signals transmitted by cell surface receptors can have different outcomes, depending on the self-adaptation of the signal transduction cascade(s).

Accordingly, their cross-reactivity with self or foreign molecules may, or may not trigger significant reactions.
III- Model: the dialectic self

The set (#1) of less intelligent and more stable cells provides the physiological referential to set #2.

The set (#2) of more intelligent and less stable cells provides the discrimination against non-self.

Set #1 slowly drifts in time, as the organism ages. Set #2 has the flexibility to adapt, while being kept in frame by set #1.
**Desensitization**

The average time between two checks of cells of type #2 by cells of type #1 provides a pace for desensitization by repeated administration of low doses.

Desensitization results from the faking of the physiological periodical re-adjustment devices causes a modification of thresholds.
Conclusions

The robustness of the self requires self-optimisation of reactivities at the single cell level.

The price to pay is periodic checks that maintain the norms.

The self is a set of self-assessed norms. Anything that falls outside this set of norms, is non-self.
The self is constantly assessed

The self non-self discrimination may vary in time.

The self non-self discrimination may also vary in space. To some extent, it may be local (e.g. liver vs lung vs gut).
Norms may have little to do with the molecular nature of reactive elements, while their local concentrations are always critical.

Failures at many different steps may have pathological consequences. Auto-immune disorders may result from the dysfunction of quality control devices as much as of primary functions *per se.*