WHAT AUTOIMMUNITY RESEARCH SUGGESTS ABOUT CANCER RESEARCH

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The seminal idea of this workshop is the exercise of placing cancer immunotherapy inside the theoretical context built by autoimmunity research.

Practical achievements of cancer immunotherapy research are not impressive. Forty years after the experiments with chemically induced sarcomas showing tumor specific rejection antigens, we still do not have a molecular description of these antigens and cancer immunotherapy in the clinical setting is limited to the intralesional application of BCG in melanoma and bladder carcinoma, and to the use of interferon in a handful of rare malignancies.

However the production of immunology knowledge is growing exponentially.

Accepting the risks of oversimplification, we could classify this production along two diverging axes:

Incremental improvements: more data that can be understood in the framework of the clonal selection theory and deletional tolerance. These data provide a better characterization of cancer antigens, specially those defined by CTL, a deeper understanding of costimulatory signals, new cancer related genes and new technologies for better vaccines and better recombinant antibodies. The consequences of these improvements are expressed in the new products currently undergoing clinical trials.

Discontinuities: data that do not fit well in the previous theoretical framework. These are basically the data about physiological self recognition, dominant tolerance, ignored autoantigens, recursive selection and the connection between innate and acquired immunity. The consequences of these emerging ideas, in terms of new products, are nowhere.

What would happen if you would look at cancer immunology wearing the glasses of autoimmunity research?

The first idea is that there is a lot of self antigens that induce neither immune activation nor tolerance. They are simply ignored, although potentially autoreactive lymphocyte clones exist. These results induced a focus shift from repertoire selection to antigen presentation.

Not only can many self antigens co-exist with their specific lymphocyte clones without activating them, but besides, there is also a physiological self recognition, which produces lymphocyte activation but not autoimmune pathology. This is another major change of viewpoint in fundamental immunology.

A third major discontinuity related to the previous ideas is that of "dominant tolerance". Three lines of evidence supported a change in our views about tolerance to "one's self".

First, experiments showed that irradiated animals reconstituted with mixed lymphocyte pools from tolerant and autoimmune donors were always tolerant and not autoimmune.

Secondly, long term tolerance induced with monoclonal antibodies behaves "infectiously". This means that it can be transferred to naive animals by transferring CD4 cells. Moreover, after two weeks the transferred cells are no longer necessary because the lymphocytes of the recipient animal had learned tolerance and had also acquired the ability to transfer tolerance to a third animal.

Finally, recent experiments with transplantation of allogeneic thymus epithelium have shown induction of tolerance to antigens from donor strains that were not present in the thymus; and this tolerance can also be transferred to a naive animal by CD4-T cells.

These data point to the idea that it is necessary to activate autoreactive cells in order to ensure lack of self aggression and tolerance.

A fourth discontinuity related to previous ideas comes from the study of the homeostatic regulation of the number of lymphocyte. The approach is to operationally divide the B-lymphocyte repertoire in three sectors: lymphocytes emerging from bone marrow, peripheral resting lymphocytes (but may be activated with LPS) and actually activated lymphocytes (Ig secreting) and then to study lymphocyte counts and repertoire diversity in each compartment.

Competition chimera experiments show that there is a selection of the repertoire occurring as lymphocytes move from the emerging, then to the available and finally to the actual repertoire; and that this selection is BCR-mediated, but antigen-independent. The obvious conclusion is that this selection is driven by interactions with components of the self.

Finally, another body of evidence comes from the links between the innate and the acquired immune system. Many immunologists see both systems as separate units or at best, linked by the use of innate immune mechanisms in the effector branch of acquired immunity.

At its early times, immunology was built around the study of responses to a handful of highly immunogenic foreign antigens. However, accumulating data from more and more antigenic compounds indicated that the immune system is really focused on part of the self and on part of the nonself; and that probably the mechanisms for this priority setting come from the innate immunity.

Several new ideas are emerging from the interpretation of these facts.

1. Most "self" antigens induce neither immunity nor tolerance. They are just "not-presented".
2. Available and actual repertoires are selected by components of the "self".
3. Part of the repertoire is a network of VRMs, connected among themselves and to self antigens; and conforming a kind of central immune system.
4. The network organization contains the "memory" of the developmental self.
5. The true distinction made by the immune system is not between self and nonself, but between "founder antigens" and latecomers.
6. The immune system does not care about self/nonself, but about the identification of danger.
7. Danger identification guides antigen presentation.

However, what is important in an emerging paradigm is not mainly if it is close to reality, but if it is fruitful. If all the precedent is at least partially true, then we could make the following provisional assumptions:

- Cancer cell components are part of the ignored "cryptic" self.
- Cancer cells do not provide enough "danger signals".
- Cancer cell "visible" components are connected to the network-regulated central immune system.
- Anti-tumor immune response is restricted by "space" in clonal competition.
- Anti-tumor immune response is restricted by dominant tolerance.

These assumptions will drive us away from the current focus on identifying more cancer antigens; and suggest to set new priorities to find:

- means to subvert dominance / crypticity hierarchy.
- means to modify the behavior of presenting cells.
- means to overcome dominant tolerance.
- means to "open room" for clonal expansion.

Taking a step forward to the experiments we could consider possibilities such as:

- to shift the interest from "visible" cancer antigens to cryptic ones.
- to try immunosuppresion for cancer treatment.
- to combine cancer vaccinations with immunosuppresive procedures.
- to include defined ligands of natural immunity into vaccine formulations.

Looking back to current successful vaccinology, what you find is a smart use of the programmed algorithm of the immune system that has been selected by evolution.

But cancer vaccinology will demand to be reprogramed.

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