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Applying the uncertainty principle to immunology

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“...it is becoming clear that a salient aspect of immune cell biology is its plasticity and ability to adapt to environmental circumstances...”

“Predictions are very difficult, particularly about the future”

—Niels Bohr 1885–1962

Immunologists have gone to extraordinary efforts to categorize immune cells according to inflexible taxonomic principles similar to those applied by Linnaeus to catalog animals and plant. Whether circulating in the blood or infiltrating tissues, immune cells are assigned to individual taxa according to highly differentiated and inflexible properties carried through cell-to-cell contact or the production of soluble factors.

“Niels Bohr's quantum theory interprets nuclear elements and their structure according to a stochastic expectation that reflects likelihood rather than certainty.”

Therefore, CD4 T cells recognize antigens and ‘help’ other cells to exert effector functions, CD8 T cells recognize antigens and kill, B cells make antibodies, macrophages incorporate particles, neutrophils kill organisms, NK cells kill autologous cells, dendritic cells present antigens. Furthermore, within each cell type there are subtypes; there are Th1, Th2 and Th17 helper T cells; regulatory subsets of CD4 and perhaps CD8 cells; and maybe subsets of B cells, and so on. However, it is becoming increasingly recognized that such classifications represent the functional status of a cell at a given time point rather than an inflexible entity; immune cells, unaware of the wealth of literature about them, behave with extraordinary plasticity that defies any basic classification. Therefore, CD4 T cells can be cytotoxic [1], NK cells may serve as ‘helpers’ for CD8 T-cell activation [2], as can B cells [3], which can also act as regulatory cells that promote escape from host protective immune function [4]. The transcription factor FoxP3, classically believed to exert regulatory functions, is also a marker of good prognosis when expressed by T cells infiltrating tumors [5–7], and the same could be said of the surprising role that the immune regulatory cytokine IL-10 plays in cancer [8]. Thus, it is becoming clear that a salient aspect of immune cell biology is its plasticity and ability to adapt to environmental circumstances, as well described for macrophage polarization [9].

Niels Bohr's quantum theory interprets nuclear elements and their structure according to a stochastic expectation that reflects likelihood rather than certainty. An electron in a carbon

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atom is likely to follow a specific orbit given a certain level of energy; however, exact measurements are difficult according to Heisenberg's uncertainty principle. To know the velocity of a quark we must measure it, and to measure it, we are forced to affect it. It could be argued that cells act in very much the same way, and to constrain their behavior within the limits of a catalogue is the same as saying that there is a type of child who eats lollipops while another enjoys running kites.

This collection of monographs looks at immunology with a dynamic perspective; the authors present a multifaceted view of immune cells as they operate in the immune activated environment. In particular, the function rather than the biological identity of immune cells is looked at as potential target for therapy. For example, Imanguli *et al.* observed that during chronic graft-versus-host disease, IL-15 is highly expressed not only by specific immune cells as it would be predicted by current views, but by all cells involved in the inflammatory process including epidermal cells [10]. Cells interact and influence each other as the inflammatory process inflates and, like the mood of a congregation, pathways may be influenced independently of cell differentiation. Therefore, it is the process rather than the identity that characterize immune function, as immune cells gradually acquire novel functions that coordinate to serve a common biological purpose. In this issue, we discuss the immune cross-talk driven by NK cells [11], the split personality of NKT cells [12] and macrophages [13] in malignancy, autoimmune disorders and infectious disease, the two-sided roles of dendritic cells in the pathogenesis and treatment of human disease [14], the pleiotropic functions of naive, effector and memory CD8 T cells [15] and tumor infiltrating lymphocytes [16] and how lymphocyte function may be influenced by the stromal cell network [17] affecting the inflammatory process [18]. We previously suggested that the same inflammation that fosters cancer growth also distinguishes cancer tissue from the rest of the organism, which in normal conditions is not inflamed [19]. Targeting the immune cells located in the inflamed tumor microenvironment, by altering their function to induce an acute inflammatory switch, may represent a logical approach to therapy [20]. Moreover, studying immune cells at the time and at the site of their function, may provide better insights regarding the aspects of their biology relevant to a given clinical phenomenon, whether it is the clearance of pathogens, the rejection of tumors, graft-versus-host disease or transplant rejection of a flare of autoimmunity. Therefore, we hope that this collection will promote a global and dynamic approach to immunotherapy, encouraging clinical and basic investigators to abandon the stiffness of the current taxonomic interpretation of immunity in favor of a malleable functional interpretation.

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