Published in final edited form as:

Curr Opin Pharmacol. 2009 August ; 9(4): 445–446. doi:10.1016/j.coph.2009.06.013.

Identification of novel immunosuppressive pathways pave the way for drug discovery

Francesco Di Virgilio and

Department of Experimental and Diagnostic Medicine, University of Ferrara, Ferrara, Italy E-mail address: fdv@unife.it

Simon C Robson

Transplantation Institute and Vascular Biology Centers at the Beth Israel Deaconess Medical Center, and the Transplant Biology Research Center at the Massachusetts General Hospital, Harvard University, Boston, MA, USA E-mail address: srobson@bidmc.harvard.edu

“And therefore as a stranger give it welcome.□ There are more things in heaven and earth, Horatio,□ Than are dreamt of in your philosophy”. Shakespeare.

“In the middle of the road of my life I awoke in the dark wood where the true way was wholly lost” or more optimistically, you chose.... “From a little spark may burst a flame.” Dante.

As we deepen our understanding of the immune system at the molecular level we realize that many more soluble immunomodulatory factors than previously anticipated are released by what are considered “immune” and “non-immune cells” that closely dictate ensuing responses. Several of these factors have overt immunostimulating activities, while others may be conveniently classified as inhibitory mediators. However, dogmatic attribution of functions is often impossible: many immunomodulatory mediators may activate or inhibit immunity and inflammation depending on the kinetics of exposure, concentrations of mediators and the concomitant presence of other extracellular factors. End results that may be quite distinct are likely facilitated by the integration at the target cell level of these multiple signals. This concept of “variability in any beginning” has been known for millennia, and associated with choice as with the two headed Roman god of gateways, Janus; or the Hindu elephant god of obstacles and beginnings, Ganesh. Immune cell interconnected networks may be functional in much the same way as the gating of signals in “flash memory” operate. These issues are particularly relevant when we move away from the cell surface and attempt to characterize the biochemical composition of the inflammatory and pericellular microenvironment, where multiple discrete compartmentalized sites are likely to exist. Consider, as an example, cancer where adenosine and factors released from tumour cells might continuously influence the responses of infiltrating immune cells, thus turning what should be a host protective effector mechanism (anti-tumour) into a detrimental (pro-tumour) response.

Several endogenous immunosuppressive factors have been recognized for decades, but the list of such factors has increased dramatically over the last few years. In addition to cytokines, we now know that many factors, including ecto-enzymes previously considered to be “inert” (e.g. arginase), are, on the contrary, endowed with a powerful immunosuppressive activity.

© 2009 Elsevier Ltd. All rights reserved.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Molecules such as nucleotides and derivatives, which were thought to be restricted to intracellular mediators, involved in biological synthetic pathways and serving as a universal energy currency, are now looked at as modulators of inflammation and immunity (with differing effects at various concentrations!). Together with the discovery of novel soluble factors, scientists in this area have also identified the cell types chiefly responsible for their release. Some times, these are well known cells that can be imparted with this novel function; at other times they are utterly new cell types, where the characterization might not be entirely satisfactory.

The obvious consequence of such a powerful research effort is the identification of many new perspective targets for pharmacological intervention. We all know that despite the wide availability of products marketed by the pharmaceutical industry, families of immunomodulatory drugs are few. In other words, all our efforts to modulate immunity revolve about a few, select targets. These limitations pose obvious limits to our ability to treat immunological and inflammatory diseases effectively. Here, we provide a concise description of the cellular biology of major novel and recognized negative modulators of immunity, underline the role of novel cell types and provide an update of putative drugs that are being tested for their ability to interfere with these pathways.

This issue provides an appraisal of a) the bifaceted action of TGF- β , IL-10 and IL-22, b) the crucial role of HLA-G in pregnancy, c) the novel field of intervention opened by the discovery of myeloid-derived suppressor cells, d) the immunoregulatory effect of hemeoxygenase and one of the products, carbon monoxide, e) insights into a fascinating world of extracellular nucleotides and nucleosides, d) the contribution to immunity of Annexin-1 and microRNAs to immunoregulation.

These discoveries of novel mediators of immunity will be relevant for therapy as well as diagnosis and prognosis. It would be highly desirable to validate a panel of easy-to-measure soluble factors or bio-markers, which might allow us to recognize inflammation early, help monitor the clinical course and allow intervention with targeted therapies, as required.

We also hope that this contribution will encourage investigators from these somewhat different fields to consider the multiple ways cells can communicate closely or at a distance in the absence of direct contacts. This early goal is perhaps the major rationale behind the choice of the themes dealt with in this issue on Immunomodulation.

Biography

Francesco Di Virgilio, M.D., is currently Professor of Clinical Pathology and Chairman of the Department of Experimental and Diagnostic Medicine at the University of Ferrara. His current research interests focus on the modulation of inflammation and innate immunity by extracellular nucleotides with particular emphasis on the role of the P2X₇ receptor.

Dr. Simon C. Robson MD, PhD, is a researcher in the Transplantation Institute and Vascular Biology Centers at the Beth Israel Deaconess Medical Center, and the Transplant Biology Research Center at the Massachusetts General Hospital, both at Harvard University in Boston. His area of basic science expertise is in the CD39 family of ectonucleotidases. These are vascular and immune cell expressed ectoenzymes that are crucial in regulating vascular inflammation and immune responses in transplanted and native organs. His laboratory, in collaboration with St. Vincent's Hospital, Melbourne, also addresses alterations in coagulation in transplantation. He was appointed as Professor in Medicine at the Harvard Medical School in 2006. He has attempted to maintain a balance between the very different roles of physician, scientist and teacher.