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Review article

Wandering pathways in the regulation of innate immunity and inflammation

Alberto Mantovani [a, b, c, *]

[a] Humanitas Clinical and Research Center, Via Manzoni 56, 20089, Rozzano, Milan, Italy
[b] Humanitas University, Via Rita Levi Montalcini, 20090, Pieve Emanuele, Milan, Italy
[c] The William Harvey Research Institute, Queen Mary University of London, Charterhouse Square, London, EC1M 6BQ, United Kingdom

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ABSTRACT

Tumor-associated macrophages (TAM) have served as a paradigm of cancer-related inflammation. Moreover, investigations on TAM have led to the dissection of macrophage plasticity and polarization and to the discovery and analysis of molecular pathways of innate immunity, in particular cytokines, chemokines and PTX3 as a prototypic fluid phase pattern recognition molecule. Mechanisms of negative regulation are complex and include decoy receptors, receptor antagonists, anti-inflammatory cytokines and the signalling regulator IL-1R8. In this review, topics and open issues in relation to regulation of innate immunity and inflammation are discussed: 1) how macrophage and neutrophil plasticity and polarization underlie diverse pathological conditions ranging from autoimmunity to cancer and may pave the way to innovative diagnostic and therapeutic approaches; 2) the key role of decoy receptors and negative regulators (e.g. IL-1R2, ACKR2, IL-1R8) in striking a balance between amplification of immunity and resolution versus uncontrolled inflammation and tissue damage; 3) role of humoral innate immunity, illustrated by PTX3, in resistance against selected microbes, regulation of inflammation and immunity and tissue repair, with implications for diagnostic and therapeutic translation.

Contents

1. Encounter with the big eaters: the good, the bad and the never ugly macrophage

I trained as a physician scientist, spending a substantial part of my time in the lab, first at the Institute of General Pathology (Molecular Biology, in pioneering early days), then at the Mario Negri Institute (immunology, Dr. Federico Spreafico). A close encounter with patients at the Istituto Nazionale Tumori in the Department lead by Gianni Bonadonna with Dr. Fossati Bellani had a profound impact on my choice of cancer as a major focus of my research [1]. I met the “big eaters”, the macrophages, as part of what was then called the “reticuloendothelial system”. A typical

* Humanitas Clinical and Research Center, Via Manzoni 56, 20089, Rozzano, Milan, Italy.
E-mail address: Alberto.Mantovani@humanitasresearch.it.

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assay was injection of india ink and measuring its clearance. I was fascinated by macrophages and therefore applied to work in the laboratory of Robert Evans and Peter Alexander. They had discovered that activated macrophages could kill tumor cells extracellularly [2]. Extracellular killing of tumor cells is a property of classically activated, or M1, macrophages. Siamon Gordon in Oxford later discovered an alternative form of macrophage activation (M2) driven by IL-4 [3]. Many groups including mine have contributed to the characterization of polarized macrophage activation [4–9]. Progress has been made in defining the molecular basis for polarized macrophages activation, including the role of members of the Stat family, NFκB, KLF4, PPARγ, Myc [6,10]. Epigenetic analysis has added a new dimension to defining the molecular landscape and mechanism involved in macrophage differentiation and polarized activation [11].

The project I was assigned at the Chester Beatty was to investigate the role of macrophages in response to irradiation. In retrospect it was an interesting subject given the role of these cells in tissue repair [12] and the recent evidence linking these cells to response to irradiation [13]. However, at the time the project did not work. At the Mario Negri Institute I had done some work on Adriamycin (now known as Doxorubicin) and therefore I decided to work on that as a side project [14,15]. I published this paper as "solo" author, because PA (short for Peter Alexander) and Bob said that it was my idea, my work, my paper: what a lesson, and more so now, at a time of diffuse honorary authorship. The role of immunity in the response to selected chemotherapeutic agents has been revamped by the studies conducted by Laurence Zitvogel and Guido Kroemer on immunogenic cell death [16].

2. Macrophages in cancer: general lessons for immunity and inflammation

After I returned to Milan I focused my attention on macrophages in really malignant mouse tumors, ie a metastatic model and ovarian cancer. The latter provided easy access to ascites, from which it was relatively easy to isolate tumor-associated macrophages (TAM). Much against current views I found that TAM promoted tumor growth *in vitro* and *in vivo* and again I published a "solo" paper [17,18]. TAM have served as a paradigm of the connection between inflammation and cancer [19,20] and illustrated the concept that the microenvironment is a key determinant of tumor progression and a target for therapeutic intervention. Studies on the connection between inflammation and cancer and on immune surveillance [21] propelled a paradigm shift in the vision of the essence of cancer from a cancer cell centric view [22] to one that includes tumor promoting inflammation and tamed adaptive immunity [19,20,23,24]. This change in vision of the essence of neoplasia has been paralleled by the development of immunotherapy strategies including targeting of TAM [13,25].

TAM have served as a paradigm for the plasticity and polarization of macrophages [4,7,12,26] under a variety of pathophysiological conditions ranging from tissue repair to autoimmunity. Mills and colleagues had used the term M-1 and M-2 referring to macrophages from two strain of mice exhibiting different properties and different propensity to mount a Th1 and a Th2 response, respectively [27]. Unfortunately, the alternative activation by IL-4 discovered by Siamon Gordon [3] was not quoted and discussed. We used M1 to refer to classically activated, tumoricidal macrophages and M2 to the IL-4 activated macrophages. TAM had M2 properties [4,7]. M1 and M2 or M2-like are extremes of a spectrum in a universe of activation states [28]. The M1/M2 (and M2-like) nomenclature mirrors Th1/Th2, ILC1/ILC2, type1/type2 immunity etc. On the other hand, macrophage (and T cell or ILC) plasticity defies a simplistic allocation to an M1 or M2 phenotype. I have argued that M1/M2 has heuristic value and that it has served as a useful communication tool within the community of immunologists and with other fields of biomedicine, as shown by its darwinian success [29]. Polarized macrophages have emerged as key players in autoimmunity as illustrated by rheumatoid arthritis [30–32].

3. The small brothers, neutrophils

In the early '80 I went back to molecular biology and decided that I had to get acquainted with the technology which was changing the landscape of research in Immunology and oncology. I went back the National Institutes of Health, which I had visited in 1978 and 1978 (Laboratory of Ronald Herberman) and spent a year in Frederick with Luigi Varesio in the lab of Joost Oppenheim. Capitalizing on that experience, in the context of a study on expression of transcription factors in myelomonocytic cells, we made the unexpected observation that neutrophils express high levels of the c-fos transcription factor [33]. This observation suggested that neutrophils were more than terminally differentiated effector cells and that they could reprogram their function. We went on to show that bacterial products and selected cytokines, IL-1 in particular, dramatically increase the lifespan of these cells, allowing time for functional reprogramming [34]. Neutrophils have since emerged as active players in induction, regulation and effector phase of diverse forms of immunity [35,36]. Moreover, evidence suggests that neutrophils can undergo polarization, N1 and N2 in tumors [37], though the signals involved are different from IL-4. It will be important to assess the role of neutrophils in autoimmunity from the more sophisticated perspective of neutrophil plasticity and their role as sophisticated regulators of immunity.

4. Negative regulators: from cancer to autoimmunity

Once upon a time there was only one cytokine related to inflammation and produced by macrophages, IL-1 [38–40] (see also review by Charles Dinarello in this issue). It was therefore natural get interested in IL-1. In parallel I had the privilege of starting an invaluable collaboration with Elisabetta Dejana, an expert in endothelial cell biology and a leader in the field. At a time of the "reticuloendothelial system", we engaged in a fruitful and enriching collaboration on the interplay between immunity and vascular endothelium. We discovered that a cytokine "bouille-à-bèsse" caused gene expression dependent reprogramming of endothelial cells and identified the active ingredient as IL-1 [41–43]. The picture which emerged from the studies conducted by us and by others (e.g. Ref. [44]) revealed that inflammatory cytokines activated a proinflammatory/prothrombotic program in endothelial cells [45]. Later, given my interest in alternative activation of macrophages, we described how IL-13 affects endothelial cell function in a distinct way [46]. Endothelial cells were once seen as a "sheet of nucleated cellophane" endowed with negative properties, ie not being thrombogenic. Therefore we witnessed a major change in the view of the pathophysiology of vascular biology and of its interplay with the immune system.

Siamon Gordon described an alternative, M2 form of macrophage activation [3]. In the context of an analysis of the interplay of IL-4 with components of the IL-1 system, we identified the type 2 IL-1 receptor (IL-1R2) as a decoy for IL-1 upregulated by IL-4 and glucocorticoid hormones [40,47]. The classic definition of "receptor" involves ligand recognition and signalling. The discovery of a decoy receptor was without precedent in biology. Decoy receptors have since emerged as a general strategy to tune the action of cytokines, chemokines and growth factors. Decoy receptors have

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