L33. Neutrophil in immunity: A key modulator

Polymorphonuclear neutrophils are “professional” phagocytic cells of the innate immune system that act as the first line of defense against invading pathogens, principally bacteria and fungi but also viruses. Because of their powerful microbicidal equipment, they have a major role in inflammatory responses other than anti-infectious defenses. However, numerous in vitro and in vivo studies, focusing on novel aspects of the neutrophil biology and function, have recently shed a new light on the potential role that neutrophils can exert in the modulation of innate and adaptive immune responses [1]. It is now unequivocal that neutrophils are not, as for long time thought, terminally differentiated cells “devoid of transcriptional and protein synthesis activity”. In fact, besides several preformed or rapidly generated inflammatory mediators, neutrophils display the capacity to de novo synthesize and release also several chemokines and cytokines with immunoregulatory properties [1,2]. It is however important to mention that, at least in vitro, neutrophils usually produce, on a per-cell basis, fewer molecules of a given cytokine than mononuclear leukocytes [2]. However, considering that neutrophils clearly pre-dominant over other cell types under inflammatory conditions in vivo, it becomes obvious that the contribution of neutrophil-derived cytokines can be of foremost importance. To date, a wide range of stimuli able to induce characteristic signatures of chemokine and cytokine synthesis by neutrophils have been identified. Considering that neutrophils usually represent the first cell type infiltrating at the site of infections, a stimulus-specific response of neutrophils in terms of cytokine production might direct the evolution of certain types of inflammatory and immune reactions to support the transition from innate to adaptive immunity.

To date, dozens of cytokines have been demonstrated as released by neutrophils in vitro, either constitutively or following appropriate stimulation, and/or in vivo, including proinflammatory, anti-inflammatory, immunoregulatory, angiogenic and fibrogenic cytokines, chemokines, and ligands belonging to the TNF superfamily. The role of these molecules in mediating various neutrophil-dependent immunoregulatory functions is partially described below. For instance, chemokines are particularly represented among the cytokines produced by neutrophils, and include those primarily chemotactic for neutrophils themselves, monocytes, DC, NK, Th1 and Th17 cells. It follows that a role for neutrophils in orchestrating the sequential recruitment to, and activation of, distinct leukocyte types in the inflamed tissue is very plausible, as already demonstrated to occur in several experimental models [1,2].

There is now wide experimental evidence that neutrophils have the capacity to modulate the migration, maturation and function of several leukocyte types including DCs, T-cells and B-cells [1]. Regarding DCs, it is noteworthy to mention that neutrophils have been shown to produce biologically active CCL20 and CCL19, two structurally related CC-chemokines that have been suggested to play a fundamental role in trafficking of, respectively, immature and mature DC to mucosal surfaces and lymphoid organs. Likewise, neutrophils release several antimicrobial compounds, such as lactoferrin, LL-37 and cathepsin G, that have been found to act as chemoattractants for immature DC [3]. In addition, neutrophils can proteolytically activate prochemerin to generate chemerin, one of the few chemokines that attracts both immature DC and plasmacytoid DC [3]. Neutrophils can also modulate DC maturation and function either through the release of several mediators or through direct physical interaction between Mac-1 (CD11b/CD18) and DC-SIGN [4]. Neutrophils also act as transport vehicle for pathogens and, in turn, deliver antigens to DC, thus playing an important role in the activation of T-cell immune responses controlled by DC [4]. Concerning the interactions between neutrophils and B-cells, of particular interest are the findings that neutrophils produce significant amounts of BLYS/BAFF (B-lymphocyte stimulator/B-cell activating factor) and APRIL (a Proliferation-Inducing Ligand), two related members of the TNF family that are well known to be essential for B-lymphocyte homeostasis [5]. Therefore, it is plausible to assume a role of neutrophils not only in sustaining B and plasma cell antibody production and survival, but also in promoting B-cell-dependent autoimmune diseases and tumors, as already elegantly demonstrated in the case of B-cell lymphoma [5]. In this context, it has been recently found that neutrophils are not only eager users, but also proficient inducers of IgG and IgA due to their ability to cross-talk with a unique subset of B-cells lodged in the marginal zone (MZ) of the spleen, in a T-cell-independent pathway [6]. Cross-talk between neutrophils and T-cells has been repeatedly described to occur during infections or other inflammatory responses and diseases. Current evidence now indicates that neutrophils exhibit a significant chemotactic effect toward Th1 or Th17 cell subsets, through the release of CCL2, CXCL9 and CXCL10 or CCL2 and CCL20, respectively [7]. Neutrophils have also a role in directing T-cell polarization, for instance through their capacity to produce the Th1-inducing cytokine, IL-12. The latter has been clearly demonstrated in mouse models, in which strong Th1-dependent T-cell responses that result in pathogen clearance are elicited upon infection with Candida albicans, Helicobacter pylori, or Legionella pneumophila. Strikingly, depletion of neutrophils reverses the Th1 responses into a predominant Th2-response, therefore making the mice susceptible to infection. Besides the neutrophil’s ability to modulate T-cell functions through the production of chemokines and cytokines, recent reports suggest that neutrophils travel to the lymph nodes during infections and express both MHC II and co-stimulatory molecules [8]. However, whether neutrophils directly acquire
Neutrophils possess antigen-presenting functions or transmit signals to naive T-cells remains still puzzling. Neutrophils have also been shown to modulate the maturation, activation and functions of NK cells, either by themselves or in cooperation with other cell types [9]. In this context, it is worth mentioning that neutrophils, by interacting with specific subsets of peripheral blood myeloid DC (e.g., 6-sulpho LacNAc+ DC, also known as slanDC) can strongly potentiate IFNγ release by NK cells [10]. Importantly, the potential pathophysiological relevance of a cell network among neutrophils, slanDC, and NK cells has been suggested by immunohistochemical studies that have revealed their colocalization in several chronic inflammatory pathologies, such as Crohn’s disease and psoriasis [10]. Finally, it has also been proposed that mature postmitotic neutrophils can also “transdifferentiate” into much-longer-lived cells with macrophage- or DC-like characteristics, which might constitute a further manner for neutrophils to act as regulatory cells of the adaptive immune response [1,3].

In view of the continuously emerging findings in the field, it is predictable that in the next years there will be the discovery of additional, unsuspected biologic features that neutrophils possess.

Disclosure of interest: the author declares that he has no conflicts of interest concerning this article.

Acknowledgements: This work was supported to MAC by grants from Ministero dell’Istruzione, dell’Università e della Ricerca (MIUR-PRIN 2009MFXE7L), and Associazione Italiana per la Ricerca sul Cancro (AIRC-IG 11782).

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Available online 26 February 2013

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http://dx.doi.org/10.1016/j.lpm.2013.01.033

L34. Neutrophils in ANCA-associated vasculitis: Still under investigation

Introduction

The pathogenesis of ANCA-associated vasculitis (AAV) is unknown but is consistent with a primary role for neutrophils in the acute injury. Neutrophils are cardinal cells in the pathophysiological process in AAV since they are both effector cells responsible for endothelial damage and targets of autoimmunity. The neutrophil granule proteinase 3 (PR3) and myeloperoxidase (MPO) are the only two main target antigens for ANCA [1]. This selectivity is surprising regarding the diversity of the proteins stored within cytosolic granules. It has been proposed that the formation of Neutrophils Extracellular Traps (NETs) that are composed of DNA extruded from dying neutrophils, which bear all the cationic granule proteins including PR3 and MPO, could be involved in the pathophysiology of AAV [2]. However, NET formation does not explain this selectivity towards PR3 and MPO. Anti-PR3 ANCA are found in sera from patients with granulomatosis with polyangiitis (GPA), which is characterized by granulomatous inflammation of the upper and/or lower respiratory tract whereas anti-MPO ANCA are present in sera from patients with microscopic polyangiitis (MPA), idiopathic necrotizing crescentic glomerulonephritis, and less frequently in Churg-Strauss syndrome, which associates late onset asthma, hypersensitivity and small vessel vasculitis.

Neutrophil activation during ANCA-associated vasculitis: role of ANCA

During the pathological course of AAV, accumulation of neutrophils at the inflammatory site is a key event initiated by the