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May NETs Contain Costimulatory Molecules?

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Short communication

Since Neutrophil Extracellular Traps (NETs) were described in 2004 by Brikmann et al., they have been attributed to other functions in addition to catching and killing microorganisms [1]. As it is known, NETs are formed by chromatin and granular proteins which after stimulation are released to the extracellular environment [2].

Myeloperoxidase and neutrophil elastase are part of these structures and are actively involved in their release. The mechanism of NET formation implicates morphological changes of Polymorphonuclear (PMN) neutrophils: after activation, flattened and attached to the substratum, the nucleus of PMN lose their shape, the nuclear envelope and granules membrane disintegrate allowing the mixing of nuclear, cytoplasmic and granular components. Elastase migrates from the azurophilic granules to the nucleus and partially degradates histones, in this way promoting chromatin decondesation, and myeloperoxidase synergizes this action [3]. Finally the plasmatic membrane ruptures and ejects the interior of the cell to the extracellular space forming NETs [4]. NETs have not only been involved as defence mechanisms, but they have also been linked to tissue damage, thrombosis [5] autoimmunity and cancer immunoediting [6]. In patients with gout it has been described the formation of NETs with sterile inflammatory stimuli from crystals of monosodium urate (MSU) [7].

Nets 'ability to lower the threshold of T cell activation has been described [8]. Costimulatory molecules are necessary for activation of T cells. The B7-1/B7- 2:CD28/CTLA-4 pathway is the best characterized T-cell costimulatory pathway [9,10]. T-cell activation requires a first signal provided by the interaction of antigenic peptide/ Major Histocompatibility Complex (MHC) with the TCR and a second signal, provided by the interaction of costimulatory molecules of Antigen Presenting Cell (APC) with CD28 of T cell [11]. The costimulation can be stimulatory or inhibitory; this depends on the receptor [12]. Interaction of CD28 by B7 molecules is necessary for the optimal clonal expansion of naive T cells. CD28-dependent costimulation of activated T cells induces expression of IL-2 and the high-affinity IL-2 receptor. Activating of naive T cells induces the surface expression of CTLA-4, another receptor for B7 molecules that binds B7 molecules with a higher affinity as compared to CD28, but its effect is to inhibit, rather than activate the T cell [13]. This is essential for limiting the proliferative response of activated T cell. TCR mediated activation of T cells in the absence of costimulation results in anergy [11]. The B7-1/B7-2:CD28/CTLA-4 pathway is known to be critical for immune response initiation and regulation. Regulatory CD4 T cells express high levels of CTLA-4, and they are involved in controlling adaptive immune responses [14].

Costimulatory molecules B7-1 (CD80) and B7-2 (CD86), which can be performed in neutrophilic granules, can be expressed in the surface under certain stimuli. Sandilands et al. describe cytoplasmic reservoirs of molecules B7: CD80 mainly within secretory vesicles and CD86 within secondary, azurophilic granules and secretory vesicles [15]. As mentioned before, NETs contain granular, nuclear and cytoplasmic elements. If costimulatory molecules CD80 and CD86 are in the neutrophil granules, may they be part of NETs? Interestingly, we found CD80 and CD86 colocalized in NETs in autologous leukocytes cultures, after lipopolysaccharide (LPS) or ovalbumin (OVA) stimulation. We stained for NE to visualize NETs. A preliminary experiment with immunological synapses in MLRs was performed to assess potential functional relevance of CD80 and CD86 colocalized in NETs (Figure 1). Further assays to evaluation of T cell responses are necessary [16].

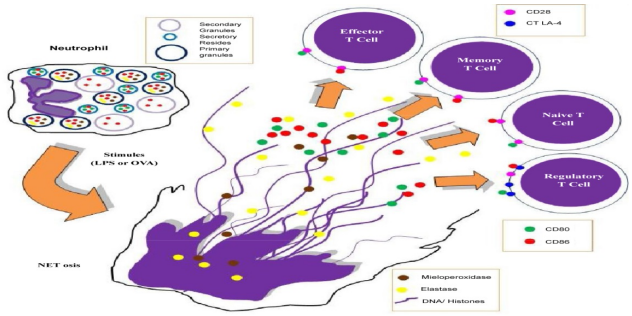

Figure 1: PMN neutrophil contains granules and secretory vesicles. Generation of NETs in autologous leukocytes cultures, stimulated with lipopolysaccharide (LPS) or ovalbumin (OVA). This would allow PMNs to exert function as APCs and modulatory functions of various subpopulations of T cells (effector, naive, memory, regulatory T cells). The presence of CD80 and CD86 in NETs could influence the cell environment through the B7-1/B7-2:CD28/ CTLA-4 pathway.

The presence of costimulatory molecules in NETs would let them influence the cell environment [16]. This finding could have relevance for a break in immune tolerance mediated by NETs. Different immunomodulatory actions could be triggered by activation B7-1(CD80)/B7- 2(CD86)-CD28/CTLA-4 pathway, resulting in stimulation, inhibition or anergy of different naive, memory and effector T lymphocyte populations. In this way, the possibility of acquiring competence to be APC by neutrophils with costimulatory molecules in NETs could link the innate and adaptive responses. These findings could also be relevant for a break in immune tolerance. Likewise, the different cell interactions and secreted cytokines also have an influence in the generation of different profiles of

proinflammatory or anti-inflammatory neutrophils. We can conclude that neutrophils could play an important role in immunomodulation.

Future research regarding the impact of NETs on the role of T cells must be performed. These new findings with the topics discussed in this communication could be the target of new therapeutic strategies in diseases where NETs and the different subpopulations of lymphocytes T are pathophysiologically responsible.

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