

## Contribution of Immunoglobulin receptor (FcγR) and proteins of complement system in neutrophil to pathogenesis and progression of Rheumatoid Arthritis

### Introduction

RA patients' blood neutrophils are functionally very different from healthy individuals' blood neutrophils: the former are primed for ROS production whilst the latter exist in a resting state in the circulation. These types of neutrophils also differ strikingly in their gene and protein expression patterns [1]. Systemic activation of the alternative complement pathway in active RA patients affects the effector functions of peripheral blood neutrophils [2]. Neutrophils from active RA and inactive RA patients responded to an exogenous complement source with significantly increased ROS production; however, incubating RA neutrophils with autologous sera indicated that there was poor FcγR/CR cooperation [2]. These results suggest that differences in the oxidative metabolism of neutrophils may reflect an acquired characteristic of the disease associated with distinct clinical manifestations.

- a) It is well established that simultaneous binding of opsonized particles to complement and Fcγ receptors enhances the efficiency of particle phagocytosis by immune cells including neutrophils. CR1 and CD32 expressed on neutrophils promote IC adherence, thereby increasing phagocytosis, oxidative burst and neutrophil degranulation compared to IC interaction with each receptor alone, providing evidence of synergy between these receptors [2].
- b) In a study of RA patients stratified according to disease activity, the level of FcγRIIIa and CR1 expression in active RA patients was higher compared to healthy controls and inactive RA patients. The cooperative ligation of these receptors led to increased O<sub>2</sub><sup>-</sup> production by neutrophils from patients with active RA. This is important because ROS are harmful mediators of autoimmune inflammation in the joints [2].
- c) More recently, it was shown that the cooperation between C5aR and FcγRs is very important to initiate and sustain neutrophil recruitment in vivo in an animal model. Specifically, C5aR activation of neutrophils is required for LTB<sub>4</sub> release and early neutrophil recruitment to the joint, whereas FcγR engagement of neutrophils induces IL-1β release, ensuring continued inflammation [3]. These data

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Short Communication

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support the concept that IC-mediated leukocyte activation is not composed of overlapping and redundant pathways but that each element serves a distinct and critical function in vivo, culminating in tissue inflammation. However, studies have highlighted the importance of CR in inflammation of articulated sites. Mice lacking the C5aR or C3aR have milder disease in arthritis models, showing that at least a part of the arthritis pathology is related to anaphylatoxin production and the interaction between anaphylatoxins and their cellular receptors [4,5].

- d) Our research team has contributed to understand the mechanism of action of antioxidant compounds on neutrophils and to develop therapeutic molecules that can modulate neutrophil ROS production in inflammatory diseases and be used in the complementary therapy in RA patients. We have investigated the in vitro pharmacological effects of natural and synthetic compounds such as flavonoids [6-8], coumarins [9,10] and sesquiterpene lactones [11] on the neutrophil ROS production and lysosomal enzyme release mediated by FcγR and CR.
- f) In the last decade, a lot of mechanisms of molecular and cellular signal transduction involved in IC deposition and in the inflammatory process have been unraveled. This information has contributed to the strategic development of modern therapies to treat inflammatory diseases in which the neutrophil has emerged as an important target of novel drugs.

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