CD38: AN ECTO-ENZYME AT THE CROSSROADS OF INNATE AND ADAPTIVE IMMUNE RESPONSES

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1. INTRODUCTION

No one would dispute that intracellular enzymes such as kinases and phosphatases play critical roles in regulating the development, activation, differentiation, and survival of lymphocytes. However, it is less well appreciated that cells of the immune system also express many membrane-associated ecto-enzymes that have the potential to regulate immune cell function. Ecto-enzymes have their active sites located on the outside of the cell and therefore must utilize substrates that are found in the extracellular milieu. Some of these enzymes, such as CD26, act as peptidases, while others, including CD73, CD38, CD39, ART2, and PC-1, utilize nucleotides as substrates. Although it was proposed that these nucleotide-utilizing enzymes might be involved in salvaging purines or in generating products such as ATP, ADP, and adenosine that function as signaling molecules for purinergic receptors, until recently very little was known about the functional roles these enzymes might play during immune responses. However, in the last 10 years it has become clear that many of these enzymes play very important roles in regulating the survival, activation, and effector function of leukocytes. Our laboratory has spent the last several years assessing the role of one of these ectoenzymes, CD38, in immune responses. In this article, we will review our recent work, focusing on the role that CD38 plays in regulating innate and adaptive immune responses.

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2. CD38 REGULATES INNATE AND ADAPTIVE IMMUNE RESPONSES

CD38 is a member of a family of enzymes that catalyze NAD glycohydrolase and ADP-ribosyl cyclase reactions. The different CD38 family members are structurally similar and members of the family have been identified from organisms as diverse as *Aplysia californica* (invertebrate sea slug), *Schistosoma mansoni* (mammalian parasite), and humans. CD38 catalyzes the formation of three products — cyclic adenosine diphosphate ribose (cADPR), adenosine diphosphate ribose (ADPR), and nicotinic acid adenine dinucleotide (NAADP) — from its substrate(s) nicotinamide adenine dinucleotide (NAD(P)). Interestingly, all three of the products generated by CD38 can induce calcium mobilization, and cADPR has been shown to regulate calcium signaling in smooth muscle, neurons, and exocrine cells. However, despite the fact that CD38 is expressed on most hematopoietic cells and can be upregulated in response to inflammatory stimuli, it was unclear whether CD38, through its production of calcium-mobilizing metabolites, could regulate immune responses.

To address this important question, CD38-deficient mice were generated in the laboratory of Maureen Howard. The initial examination of these mice indicated that CD38 was not obligatory for the development of any of the hematopoietic lineages but was necessary for optimal T cell-dependent humoral immune responses. Interestingly, the CD38-deficient (CD38KO) mice were unable to produce antibody in response to vaccination when low doses of a relatively weak adjuvant (alum) were used but responded normally when immunized with Freund’s adjuvant. At the time we proposed that CD38 might function to regulate B cell activation by acting as a co-receptor for the B cell receptor (BCR). However, subsequent experiments indicated that CD38KO B cells proliferated normally in response to BCR ligation and that the defective humoral immune response seen in the CD38KO mice was not due to the loss of CD38 on B lymphocytes. Thus, while it was clear that CD38 did regulate humoral immune responses, we had few clues as to how CD38 or its enzymatic products might function in the immune system.

2.1. CD38 Regulates Neutrophil Migration and Lung Inflammatory Responses

Since CD38KO mice made defective humoral immune responses when antigen dose and adjuvant were limiting, we considered the possibility that CD38KO mice might have difficulty in responding to the innate signals that trigger humoral immune responses. To test this hypothesis, we determined whether CD38KO mice were able to generate a normal inflammatory response. In one set of experiments, we infected CD38KO mice with the gram-positive organism *S. pneumoniae* and measured the inflammatory response. Interestingly, despite the fact that the infected CD38KO mice upregulated expression of inflammatory