A Natural History of the Human CD38 Gene

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INTRODUCTION

In the beginning, CD38 (gene symbol CD38) was but one of a handful of thymic lymphocyte surface markers [1]. It was subsequently found to be expressed also by B cells, monocytes and natural killer cells, as detailed in [2]. In immunocytes, it emerged that engagement of CD38 by specific monoclonal antibodies could command a variety of responses such as activation and cytokine release in T cells [3, 4], modulation of B cell antigen receptor responses [4], B and myeloid cell apoptosis [6, 7], modulation of the superantigen response in monocytes [7] and induction of NK cell activation and cytotoxicity [9,10]. In addition, CD38 can influence immunocyte adhesion to endothelium [10] through a counterreceptor identified as CD31 [11], leaving no doubts about the receptorial nature of CD38. The intracellular pathways activated via CD38 are being characterized and numerous cytoplasmic substrates have been identified that undergo phosphorylation following CD38 signaling [12-16].

However, the most surprising turn of events was sparked by the 1992 finding of amino acid sequence similarity between CD38 and ADP ribosyl cyclase, a soluble enzyme found in the mollusk Aplysia [17]. CD38 was found to have a complex enzymatic activity that can synthesize cyclic ADP ribose (cADPR) and nicotinic acid adenine dinucleotide phosphate (NAADP), two calcium-releasing messengers, or adenonsine 5' diphosphoribo (ADPR) [18], which plays crucial roles in ion channel gating [19] and post-translational protein modification [20]. Novel biological activities mediated by CD38 enzymatic activity emerged such as the regulation of insulin secretion [21] and neutrophil clearance of bacteria in sepsis [22].
As experimental evidence independently supports the receptor-mediated mechanism of action and the enzymatic activity, we can add CD38 to the growing list of two-in-one proteins that, aside from many leukocyte receptor-ectoenzymes, includes the TRP (transient receptor potential) cation channel LTRPC2 [19], which is both ion channel and protein kinase, and migration inhibitory factor (MIF), a secreted macrophage protein that is a cytokine with tautomerase enzymatic activity [23].

Molecular phylogenetics should give us some clues toward understanding the biological role of CD38 by suggesting how and why the receptorial and enzymatic activities co-evolved, and will be dealt with in the final part of this chapter. However, the beginning is dedicated to the structure and regulation of the human CD38 gene in view of its increasing repercussions in human physiology and biochemistry in health and disease.

THE GENESCAPE

With the availability of the first draft of the human genome the CD38 neighborhood, located at the 4p15 chromosomal region [24], is now reasonably well delineated. The organization of the CD38 locus and its surroundings, presented in Fig. 1, is based on the nucleotide sequence of a 576,121 base pair (bp) genomic segment from the GenBank database (accession number NT_027004). Proceeding from telomere to centromere, upstream of CD38 lies an important neighbor because CD157 (BST-1, BP3) is a paralog of CD38. These two genes have exquisitely similar intron-exon organization as a consequence of their origin by gene duplication [25-27]. CD38 lies approximately 50 kb downstream of CD157, with both genes having the same 5'→3' orientation. However, CD157 and CD38 may not be contiguous since, according to in silico analysis, another gene lies between them, identified only as LOC132699. The hypothetical product of this gene is a protein (accession number MGC5629) which is very similar to high-mobility group protein 17 (HMG-17), a non-histone chromosomal protein that binds to nucleosomes and enhances transcription [26].

About 86 kb downstream of CD38 are another couple of paralogous genes: HBP17 and Ksp37. HBP17 (heparin-binding growth factor binding protein), is a 17 kDa protein first identified in conditioned medium of human epidermoid carcinoma cells [27] encoded by a small, two-exon gene that is followed ~21 kb downstream by the similarly organized gene encoding Ksp37. This is a recently-described secreted protein found in human serum whose expression is limited to cytotoxic lymphocytes, be they NK or T cells [28].