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Review

Unravelling novel functions of the endosomal transporter mannose 6-phosphate/insulin-like growth factor receptor (CD222) in health and disease: An emerging regulator of the immune system

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ABSTRACT

Properly balanced cellular responses require both the mutual interactions of soluble factors with cell surface receptors and the crosstalk of intracellular molecules. In particular, immune cells exposed unceasingly to an array of positive and negative stimuli must distinguish between what has to be tolerated and attacked. Protein trafficking is one of crucial pathways involved in this labour. The approximately > 270-kDa protein transporter called mannose 6- phosphate/insulin-like growth factor 2 receptor (M6P/IGF2R, CD222) is a type I transmembrane glycoprotein present largely intracellularly in the Golgi apparatus and endosomal compartments, but also at the cell surface. It is expressed ubiquitously in a vast majority of higher eukaryotic cell types. Through binding and trafficking multiple unrelated extracellular and intracellular ligands, CD222 is involved in the regulation of a plethora of functions, and thus implicated in many physiological but also pathophysiological conditions. This review describes, first, general features of CD222, such as its evolution, genomic structure and regulation, protein structure and ligands; and second, its specific functions with a special focus on the immune system.

1. Introduction

The schemes, as they are shown in various immunology textbooks, usually portray 'sequel' events of molecular pathways with individual components at the right time in the right place – 'ready-steady- go' for their race to come. However, it goes without saying that before runners kneel down into starting blocks they must have been transported therein somehow. In other words, to allow correct cellular function it is essential to control the temporal and spatial distribution of proteins within the cell. Protein trafficking is of special importance in the context of immune cells which have to promptly react to a certain stimulus to combat pathogens and, at the same time, avoid unwanted tissue disturbances. The protein transportation system, which is crucial for maintaining cell functional integrity and thus homeostasis, presents 'prequel' events to specific responses of immune cells.

The late endosomal molecule CD222, also known as the cation-independent mannose 6-phosphate/insulin-like growth factor 2 receptor (M6P/IGF2R, CIMPR), is one of the central protein transporters [1]. It is expressed ubiquitously in the vast majority of higher eukaryotic cell types. The receptor is present mostly intracellularly, namely in the Golgi apparatus, early and late endosomes; however, it constitutively recycles between these organelles and the cell surface [2] . Its trafficking is driven by several sorting signals encompassed in the cytoplasmic domain of CD222. The extracellular domain contains several binding sites for structurally unrelated ligands and membrane partners. By virtue of its multiple binding capacities CD222 exerts a plethora of functions in protein trafficking, internalization, lysosomal biogenesis, regulation of cell growth, apoptosis and cell migration [3]. Recently, important roles have been attributed to CD222 in controlling cellular responses in the adaptive immune system. This review describes the structure and functions of CD222, and specifically focuses on its recently unravelled functions, particularly in immune cells.

Abbreviations: AP, 1 adaptor protein 1; CCV, clathrin-coated vesicles; CD-M6PR, cation-dependent mannose 6-phosphate receptor; CIMPR, cation-independent mannose 6-phosphate receptor (M6P/IGF2R CD222); DMR, differentially methylated region; LTGFβ, latent transforming growth factor β; M6P, mannose 6-phosphate; IGF2, insulin-like growth factor 2; M6P/IGF2R, mannose 6-phosphate/insulin-like growth factor 2 receptor (CD222 CIMPR); TACE, tumour necrosis factor α-converting enzyme (ADAM17); TGN, trans-Golgi network; uPAR, urokinase-type plasminogen activator receptor (CD87)

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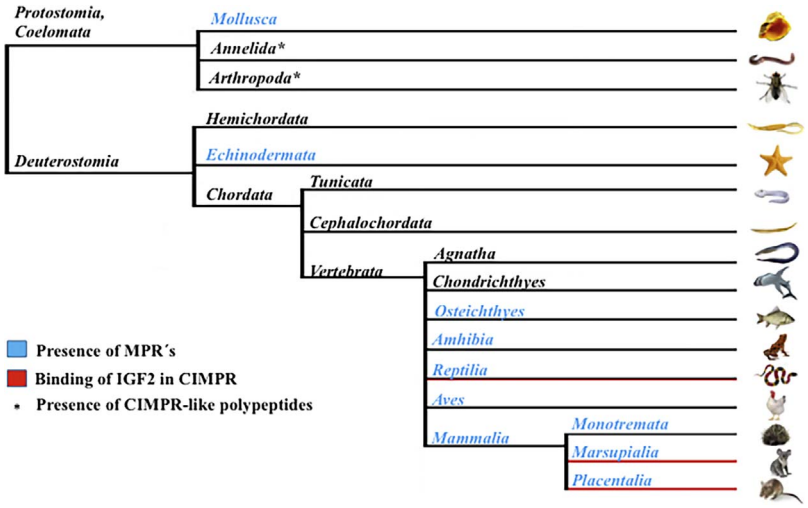

Fig. 1. *An evolutionary tree of MPR's and IGF2 binding to CD222.* CD222 (CI-MPR) appears first in *Mollusca* – namely, its presence was confirmed in the genus *Unio*. In *Annelida* and *Arthropoda,* only CI-MPR-like polypeptides were discovered. In *Asteroidea* (phylum *Echinodermata*), CI-MPR and CD-M6PR are conserved. Both receptors were also found in the classes *Osteichthyes, Amphibia, Reptilia, Aves* and *Mammalia* of the phylum *Vertebrata*. The IGF2 binding site is conserved only in *Marsupialia* and *Placentalia*. The latest study confirms the IGF2 binding also in *Reptilia* [14].

2. Evolution of the CD222 molecule

In invertebrates, putative mannose 6- phosphate (M6P) binding proteins have been found in the mollusc *Unio* [4], the common fruit fly *Drosophila melanogaster* [5] , and the starfish *Asteria rubens* [6]. In vertebrates, the fish CD222 molecule has been found to be 50% identical to the mammalian receptor [7,8]. In amphibians, reptiles, and birds, CD222 displays a higher conservation, e.g. the chicken receptor shows 60% sequence identity with the human homolog. In mammals, the nucleotide and amino acid sequence of CD222 is highly conserved [9]. Around 80% of the bovine, rat and mouse amino acid sequences are identical to the human one.

Sequence alignment studies have shown that the M6P-binding sites of CD222 are highly conserved among multiple species [10]. Hence, the binding of glycosylated ligands represents the most primordial binding capacity of CD222, shared by sauropods and synapsids 300 million years ago [11]. In contrast, the M6P-independent insulin-like growth factor 2 (IGF2) binding site evolved in vertebrates [12–14] before the appearance of imprinting in *Theria*, a subclass of mammals that include Marsupialia and Placentalia, and the IGF-2 binding capacity have remained in all lineages of primitive mammals [11] (Fig. 1).

3. Genomic structure and regulation of the CD222 molecule

The human *CD222* gene is situated on chromosome 6 (6q26), contains 50 introns and 48 exons, and spans a region of 136 kb [15–17] . The mouse *CD222* gene is mapped on chromosome 17 with a length of 93 kb and has the same number of exons as the human gene [16,18] . In rodents, CD222 is inherited maternally and repressed at the paternal locus [19], whereas IGF2, one of the major ligands of CD222, is imprinted maternally and expressed exclusively from the paternal inherited allele [18,20]. The primordial form of CD222 was originally not imprinted in ancient birds and reptiles [11]. The opposed imprinting of CD222 and IGF2 appeared in primitive mammals, remained conserved in rodents, kangaroos and opossums [11], and was lost in hominids [21]. As a result, the expression of human CD222 is biallelic [16,18], whereas the expression of IGF2 is mainly monoallelic [11]. However, monoallelic expression of CD222 was detected in some types of human tumours [22]. The imprinting of CD222 is based on the epigenetic regulation. The *CD222* gene encompasses two differentially methylated regions: differentially methylated region 1 (DMR1) that lies in the upstream promoter region, and differentially methylated region 2 (DMR2), a part of the downstream promoter. In the paternal allele, DMR1 is methylated and silenced whereas DMR2 is unmethylated and active. The unmethylated DMR2 allows transcription of the antisense non-coding RNA that participates in silencing of the paternal allele. In the maternal allele, DMR1 is unmethylated and active whereas DMR2 is methylated which results in transcription of the *CD222* gene. In the biallelic expression, the methylation of the upstream promoter region is absent [23].

CD222 is expressed ubiquitously in all tissues and cell types of the human body [15]; however, its expression level is regulated individually within diverse tissues and developmental stages [24,25]. The proximal promoter region contains binding sites for the transcription factors c-Myc, Sp1, Egr1, Krox24 and NGF-IA, which enhance CD222 gene expression [26,27].

4. Structure of the CD222 molecule

CD222 is an approximately > 270-kDa type I transmembrane glycoprotein [28] . Its N-terminal extracellular domain consists of 15 approximately 147 amino-acid-long homologous repeats with around 16–38% identity. Further, the extracellular domain possesses 19 potential glycosylation sites that do not seem to be essential for ligand binding in rodents. The cysteine residues are involved in intramolecular disulfide bonds and are essential for the proper folding of CD222 [25,29]. It has been suggested that extracellular repeats 1–9 form three-domain assemblies, whereas repeats 10–15 are sequentially arranged [30]. The transmembrane domain links the ectodomain with the C-terminal cytoplasmic domain composed of a variety of sorting signals that might be modified by phosphorylation and palmitoylation [3,16,28,31]. In the plasma membrane, CD222 appears to be organized as a dimer, primarily in the presence of its extracellular ligands [25]. Studies with truncated versions of CD222 have revealed that domains 13–15 are essential for the dimerization [30]. In detergents, CD222 is solubilized as a monomer [25]. Notably, CD222 is homologous to the approximately 46 kDa cation-dependent mannose 6- phosphate receptor (CD-MPR), and these two receptors represent the only members of the p-type lectin family [3,25,29,32,33].

5. Ligands of the CD222 molecule

CD222 binds and transports ligands containing M6P moieties on their carbohydrate side chains [3]. The four distinct M6P-binding sites are localized in the extracellular repeats 3, 5, 9 and 15 [34]. Via M6P, CD222 recognizes and binds, together with CD-M6PR, lysosomal enzymes, such as acid hydrolases, for their transportation from the trans-Golgi network (TGN) to their final destination in lysosomes [3]. Moreover, CD222 also binds extracellular M6P-bearing ligands, such as leukaemia inhibitory factor [35], granzyme B [36], latent transforming growth factor β – LTGFβ [37], proliferin [38,39], or prorenin [40]. Thyroglobulin and DNase I, that also contain M6P moieties, are bound