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Review

Scavenger receptor CD163, a Jack-of-all-trades and potential target for cell-directed therapy

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ABSTRACT

Scavenger receptor CD163 contains nine scavenger receptor cysteine-rich (SRCR) domains and because of the presence of this ancient and highly conserved protein motif, CD163 belongs to the SRCR superfamily. Expression of CD163 is restricted to cells of the monocyte/macrophage lineage and is tightly regulated, with a general tendency of anti-inflammatory signals to induce CD163 synthesis, while pro-inflammatory signals rather seem to downregulate CD163 expression. The first-identified and most-studied function of CD163 is related to its capacity to bind and internalize haemoglobin–haptoglobin (HbHp) complexes. Later on, its functional repertoire was expanded, with the identification of CD163 as an erythroblast adhesion receptor, a receptor for tumour necrosis factor-like weak inducer of apoptosis (TWEAK), as well as a receptor for distinct pathogens encompassing bacteria and viruses. Interaction of one of these ligands with CD163 might result in receptor-mediated endocytosis, but might as well trigger a signalling cascade leading to the secretion of signalling molecules, which implicates that CD163 also acts as an immunomodulator. Not only the membrane-bound form of CD163 has an immunomodulating capacity, but also soluble CD163, which is generated via ectodomain shedding, is able to exert anti-inflammatory effects. Furthermore, the concentration of this soluble protein is significantly increased under specific pathological conditions, making it a useful marker protein for certain diseases. Finally, its restricted expression pattern and potential to internalize make CD163 an attractive candidate as gateway for cell-directed (immuno)therapy. This review aims to summarize current knowledge on CD163's biology and its different biological functions beyond HbHp scavenging, thereby mainly focussing on the more recently discovered ones. Furthermore, current data supporting the capacity of CD163 to serve as a diagnostic marker in certain diseases and its potential as a target molecule for cell-directed therapy are surveyed.

1. Introduction

Macrophages and their progenitor cells, monocytes, are key players in the immune system where they fulfil a myriad of functions aided by a vast repertoire of surface molecules. Scavenger receptor CD163 is one of them and was initially identified as RM3/1 in 1987 (Zwadlo et al., 1987) before receiving its CD number in 1996 (Kishimoto et al., 1997). Different antibodies were raised against CD163 prior to its cloning and proper characterization, resulting in a series of different names for the same protein. Besides its most commonly used name CD163, this scavenger receptor is also known as Ki-M8 (Radzun et al., 1987), Ber-MAC3 (Backe et al., 1991), GHI/61 and SM4 (Pulford et al., 1992), RM3/1 (Zwadlo et al., 1987), ED2 antigen (Dijkstra et al., 1985), AM-3K (Komohara et al., 2006; Zeng et al., 1996), 2A10 (Sanchez et al., 1999), along with p155 (Morganelli and Guyre, 1988), M130 (Ritter et al., 1999), and haemoglobin scavenger receptor (HbSR) (Kristiansen et al., 2001).

Only in 2001 however, a function could be attributed to CD163 when this glycoprotein was identified as internalization receptor for haemoglobin–haptoglobin (HbHp) complexes (Kristiansen et al., 2001). This function of CD163 has been the subject of extensive investigation, as discussed in several reviews (Ascenzi et al., 2005; Fabriek et al., 2005; Graversen et al., 2002; Nielsen and Moestrup, 2009; Nielsen et al., 2010; Onofre et al., 2009; Schaer et al., 2007; Zuwala-Jagiello, 2006). Meanwhile however, also other CD163 ligands were described, indicating that CD163 is a multifunctional receptor involved in receptor-mediated endocytosis and in signalling pathways upon interaction with diverse ligands. This review aims to summarize current knowledge on CD163's biology and its different biological functions beyond HbHp scavenging, thereby mainly focussing on the more recently discovered ones. Furthermore, current data supporting the capacity of CD163 to serve as a diagnostic marker in certain diseases and

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its potential as a target molecule for cell-directed therapy are surveyed.

2. Classification: scavenger receptor cysteine-rich superfamily group B

Scavenger receptor (SR) biology originated in 1979, when Brown and Goldstein explored the uptake of modified low-density lipoprotein (LDL) by macrophages. At present, the term SR defines a vast number of glycoproteins involved in the recognition of polyanionic structures of either endogenous (e.g. oxidized or acetylated LDL) or exogenous (e.g. bacterial lipopolysaccharides (LPS)) origin. Although functionally related, SR are structurally quite diverse, containing, among others, collagenous, C-type lectin, leucine-rich repeat or scavenger receptor cysteine-rich (SRCR) domains. Based on the multidomain structure, the SR family can be classified into eight different classes (A–H) (Areschoug and Gordon, 2009; Krieger, 1997; Krieger and Herz, 1994; Murphy et al., 2005; Pluddemann et al., 2007; Taylor et al., 2005).

The first SR to be cloned was the class A scavenger receptor SR-AI that is composed of several distinct domains including a C-terminal SRCR domain (Freeman et al., 1990). At present, this domain has been found in more than 25 proteins, including CD163, and its presence is the molecular signature of the so-called SRCR superfamily (SRCR-SF) as nicely reviewed by Sarrias et al. (2004). Sequences containing the SRCR domain have been identified in representatives of diverse animal phyla, ranging from marine sponges (Blumbach et al., 1998; Pancer et al., 1997) and insects (Gorman et al., 2000), to avian (Gobel et al., 1996; Iwasaki et al., 2001; Koskinen et al., 2001), amphibian (Goldberger et al., 1987; Yamada et al., 2000), and various mammalian species (Aruffo et al., 1991; Holm et al., 2009; Mackay et al., 1986; Nunes et al., 1995; Polfliet et al., 2006; Takito et al., 1996). Notwithstanding the structural relationship due to the presence of this ancient and highly conserved protein motif, there is, as yet, no unifying biological function for the SRCR-SF (Sarrias et al., 2004).

The SRCR domain is an extracellular domain consisting of 100–110 amino acid residues (Sarrias et al., 2004). The SRCR-SF can be divided into two groups (A and B), depending on the number of cysteine residues present in the SRCR domains, and, consequently, on the disulphide-bond pattern established. Another distinguishing feature is the number of exons coding for each SRCR domain. Group A SRCR domains contain 6 cysteine residues and are encoded by two exons, whereas those of group B contain 6 or 8 cysteine residues and are encoded by a single exon. Protein alignment and studies on the cysteine disulphide linkage pattern of several members of the SRCR-SF have shown that the relative position of cysteines and their disulphide bond pattern are well conserved within each SRCR domain. Thus, according to the usual nomenclature for numbering cysteines 1–8 of group B domains, the disulphide pattern of an SRCR domain is C1–C4, C2–C7, C3–C8, and C5–C6. Cysteines C1 and C4 are absent in group A domains, though always present in group B domains. Some group B domains lack the C2–C7 bridge (Resnick et al., 1994; Sarrias et al., 2004). CD163 is composed of nine type B SRCR domains (SRCR1–9) all containing four disulphide bridges except for SRCR8, which lacks the C2–C7 bridge (Fig. 1).

Members of the group B SRCR-SF are further divided into different subgroups based on their structure, sequence homology, and extracellular domain organization (Gronlund et al., 2000; Sarrias et al., 2004). The first and most extensively studied subgroup comprises CD5 (Jones et al., 1986), CD6 (Aruffo et al., 1991) and Spα (Gebe et al., 1997), which all contain three SRCR domains. The second subgroup presents SRCR domains that are part of a multidomain mosaic extracellular region, and includes, among others, gp-340/SAG/DMBT1 (Holmskov et al., 1997; Ligtenberg et al., 2007; Mollenhauer et al., 1997). Members are characterized by the presence of additional domains other than the SRCR domain, such as epithelial growth factor (EGF) domain, zona pellucida (ZP) domain, fibronectin domain, etc. The third subgroup contains CD163 (Law et al., 1993) together with CD163-L1 (Gronlund et al., 2000), WC1 (Mackay et al., 1986; Wijngaard et al., 1992) and SCART (Table 1) (Holm et al., 2009; Kisielow et al., 2008). They are characterized by the presence of a long-range repeat of 5 consecutive SRCR domains with a small linker domain between the second and third SRCR domain. This long-range repeat is referred to as [b-c-d-e-d] cassette (Fig. 1). It has been suggested that CD163 emerged from CD163-L1 by gene duplication, and that during this process 3 of the first 6 SRCR domains of CD163-L1 were lost (Gronlund et al., 2000; Stover et al., 2000).

3. Structure

CD163 is a type I transmembrane protein composed of 9 extracellular consecutive SRCR domains type B, with only SRCR 6 and 7 separated by a proline-serine-threonine rich (PST) polypeptide of approximately 35 amino acids (Fig. 1). Following the SRCR domains, a short PST linker domain connects SRCR 9 with a transmembrane domain and an intracellular cytoplasmic tail. This intracellular tail is subject to alternative splicing resulting in various CD163 isoforms that differ in the length of their cytoplasmic tail (Law et al., 1993; Ritter et al., 1999). The most abundant form has a tail of 49 amino acids, while the less abundant forms have a tail of 84 or 89 amino acids. The first 42 amino acids after the membrane-spanning segment are in common for the three isoforms and this region contains consensus sequences for phosphorylation with protein kinase C and creatine kinase. Additional phosphorylation sites are present in the remaining part of the cytoplasmic tail of the isoforms with 84 amino acids. Furthermore, the common membrane-proximal region of the cytoplasmic tail includes a hydrophobic internalization motif of the type Yxxϕ, where ϕ represents a bulky hydrophobic residue (Nielsen et al., 2006). The observed mass of human CD163 under non-reducing conditions is 110 kDa, and 130 kDa under reducing conditions (Pulford et al., 1992). CD163 is extensively glycosylated, predominantly with N-linked glycans as shown by a reduction in molecular weight after endoglycosidase F treatment (Fabriek et al., 2007b; Hogger et al., 1998b).

Recently, the crystallographic structure for a group B SRCR-SF member was determined. More precisely, the N-terminal (Garza-Garcia et al., 2008) and the C-terminal (Rodamilans et al., 2007a,b) SRCR domains of human CD5 were analyzed (Fig. 1). SRCR domains have a compact fold consisting of a curved six/seven-stranded β-sheet cradling an α-helix. The structure core is formed by the association of helix α1 with a curved four-stranded antiparallel β-sheet, which includes β1, β2, β4 and β7. The three additional β-strands (β3, β5, and β6) form another antiparallel β-sheet at the bottom of the domain core, as depicted by Rodamilans et al. (2007b). For comparison with other SRCR domains, the only information available comes from M2BP (Hohenester et al., 1999), hepsin (Somoza et al., 2003) and MARCO (Ojala et al., 2007), which all belong to the group A SRCR-SF. At the sequence level, the only consistent difference between group A and group B SRCR domains is the C1–C4 disulphide bond present in group B and absent in group A. Based on the 3D structures available, this disulphide bond does not appear to have a major role in shaping the SRCR fold. Main differences are observed at the connecting loops, though overall type A and B SRCR domains share a similar fold with most of the secondary elements conserved (Garza-Garcia et al., 2008; Rodamilans et al., 2007b).