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Review

Biochemistry and cell biology of mammalian scavenger receptors

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Abstract

Scavenger receptors are integral membrane proteins that bind a wide variety of ligands including modified or oxidised low-density lipoproteins, apoptotic cells and pathogens. Modified low-density lipoprotein accumulation is thought to be an early event in vascular disease and thus scavenger receptor function is critical in this context. The scavenger receptor family has at least eight different subclasses (A–H) which bear little sequence homology to each other but recognize common ligands. Here we review our current understanding of the scavenger receptor subclasses with emphasis on their genetics, protein structure, biochemical properties, membrane trafficking, intracellular signalling and links to disease states. We also highlight emerging areas where scavenger receptors play roles in cell and animal physiology.

Keywords: Scavenger receptor; Oxidised LDL; Secretion; Internalisation; Intracellular signalling

Contents

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1. Introduction

Vascular diseases account for nearly 50% of the mortality rate in industrialised countries and are rapidly becoming a major burden in large populous countries, such as India and China [1]. Keynote studies by Brown and Goldstein led to the discovery that some patients with familial hypercholesterolaemia have mutations in the low-density lipoprotein receptor (LDL-R) that binds low-density lipoprotein (LDL) [2]. The link between elevated levels of serum LDL and cholesterol in heart disease was further strengthened by the discovery that modified LDL uptake by macrophages is linked to foam cell formation in vitro [3]. These cholesterol-filled foam cells are a major constituent of atherosclerotic plaques and lesions that form within the walls of blood vessels.

Modified LDLs are thus implicated as early causative agents in vascular disease. LDL deposits, which accumulate in vascular tissues under pathological conditions, are rapidly converted to modified or oxidised LDL (OxLDL) via nucleophilic attack by reactive molecular species that include superoxide, hydrogen peroxide and hydroxyl radicals. These reactive species are generated by the endothelium, smooth muscle tissue and migratory lymphocytes [4]. LDL modification involves changes to both protein and non-protein moieties on the LDL particle [5,6]. Central to the oxidation of LDL is a lipid peroxidation chain reaction initiated and driven by free radicals [7]. In this process, lipid hydroperoxides are formed that fragment to reactive aldehydes, such as malondialdehyde and 4-hydroxynonenal. These can then conjugate to the ε-amino groups of apoB-100 lysine residues and to amino phospholipids, such as phosphatidylethanolamine and phosphatidylserine [8]. ApoB-100 also undergoes extensive breakdown during LDL modification that is due to non-enzymatic oxidative cleavage. Histidine, lysine and proline residues are particularly susceptible to oxidative damage [9].

Modified LDL binds to a diverse range of transmembrane proteins, collectively termed scavenger receptors, which are also capable of binding a diverse variety of lipid and lipoprotein-based ligands. The scavenger receptor family can be broadly classified into eight classes (A–H) (Fig. 1). In addition to mammalian species, scavenger receptors have also been identified in nematodes and flies. In this review, we will highlight the role played by each receptor in mammalian physiology by reviewing gene organisation, tissue expression, structure, ligand specificity, membrane trafficking, intracellular signalling and pathophysiology.

2. Class A scavenger receptors

2.1. Genetics and expression

The class A scavenger receptors comprise three related genes that encode at least five polypeptides, termed SR-AI, SR-AII, SR-AIII, macrophage receptor with collagenous structure (MARCO) and scavenger receptor with C-type lectin (SRCL) [10–15]. The human SR-A (MSR1) gene is located on chromosome 8 and alternative RNA splicing can generate at least three protein isoforms, termed SR-AI, SR-AII and SR-AIII. The MARCO gene encodes a larger polypeptide and is located on human chromosome 2. The human SRCL gene is located on chromosome 18 and can be alternatively spliced to generate at least 2 different isoforms, both of which are larger than SR-A and MARCO gene products. All three genes share a common collagen-like domain suggesting that they arose from a primordial ancestral gene that underwent duplication and dispersal through the human genome during evolution. Intriguingly, the SRCL gene has ‘collected’ a C-type lectin domain that may be used by this Class A gene product for novel ligand-binding properties in comparison to the SR-A and MARCO gene products.

SR-A isoforms are largely expressed on macrophages but can also be detected on endothelial and smooth muscle tissues. OxLDL induces upregulation of SR-A mRNA levels and increases 30-fold the uptake of acetyl LDL in smooth muscle cells. Macrophage colony-stimulating factor (M-CSF) increases SR-A protein levels greater than 2-fold as well as prolonging the half-life and cell surface expression of the synthesised receptor, leading to a 1.7–3-fold increase in the uptake of acetylated LDL (AcLDL). Additionally, treating the monocytic cell line THP-1 with phorbol ester induces SR-A expression and AcLDL degradation, both of which are absent in untreated cells. However, tumour necrosis factor α (TNFα), *N*-acetylcysteine, interferon-γ (IFN-γ) and transforming growth factor-β1 (TGF-β1) cause 70, 25, 50 and 50% reduction in AcLDL binding, respectively, through a reduction in SR-A mRNA levels [16–23]. MARCO expression is detected largely on macrophages from the spleen marginal zone and lymph nodes; this receptor is also detected on splenic dendritic cells [12,24]. Binding of lipopolysaccharides, bacteria or dead or apoptotic cells increases cell surface expression and mRNA levels of MARCO [25,26], thus implicating this receptor in host defence linked to cellular and pathogenic clearance. SRCL is expressed on endothelial