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Review

Sorting an LDL receptor with bound PCSK9 to intracellular degradation

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ABSTRACT

Objective: This article reviews the mechanism by which the low density lipoprotein receptor (LDLR) that has bound proprotein convertase subtilisin/kexin type 9 (PCSK9), is rerouted to intracellular degradation instead of being recycled.
Methods: A search of relevant published literature has been conducted.
Results: PCSK9 binds to the LDLR at the cell surface. It is the catalytic domain of PCSK9 that binds to the epidermal growth factor repeat A of the LDLR. The LDLR:PCSK9 complex is internalized through clathrin-mediated endocytosis. Due to an additional electrostatic interaction at acidic pH between the C-terminal domain of PCSK9 and the ligand-binding domain of the LDLR, PCSK9 remains bound to the LDLR in the sorting endosome. As a consequence, the LDLR fails to adopt a closed conformation and is degraded instead of being recycled. The mechanism for the failure of the LDLR to recycle appears to involve ectodomain cleavage of the extended LDLR by a cysteine cathepsin in the sorting endosome. The cleaved LDLR ectodomain will be confined to the vesicular part of the sorting endosome for degradation in the endosomal/lysosomal tract.
Conclusion: Ectodomain cleavage of an LDLR with bound PCSK9 in the sorting endosome disrupts the normal recycling of the LDLR.

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Contents

1. LDL receptor-mediated endocytosis

Approximately 70% of plasma cholesterol is carried in low density lipoprotein (LDL) [1], and high levels of LDL cholesterol are a major risk factor for coronary heart disease. LDL is cleared from plasma by binding to the cell-surface LDL receptor (LDLR) and is internalized by LDLR-mediated endocytosis [2] (Fig. 1). The importance of the LDLR in cholesterol metabolism is illustrated by the severe hypercholesterolaemia in subjects who lack LDLRs [2].

The LDLR is a Type 1 transmembrane protein and has five domains [3–5] (Fig. 1). The amino terminal ligand-binding domain consists of seven repeats of approximately 40 amino acids each. The epidermal growth factor (EGF) precursor homology domain of approximately 400 amino acids consists of two 40 amino acid repeats, EGF-A and EGF-B, a 280 amino acid β-propeller and a third 40 amino acid repeat, EGF-C. The O-linked sugar domain consists of 58

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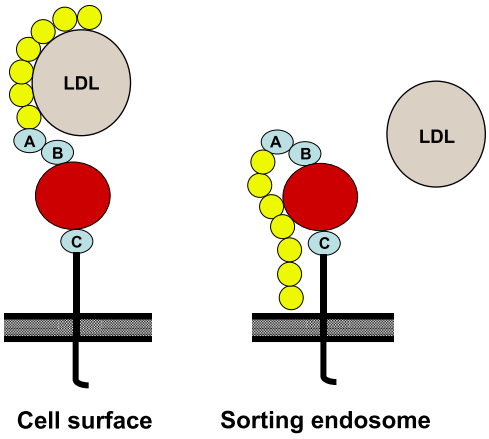

Fig. 1. The normal function of the LDLR. The ligand-binding domain of the LDLR with its seven ligand-binding repeats, is shown in yellow. The EGF-A, EGF-B and EGF-C repeats of the EGF precursor homology domain are shown in blue and the β-propeller is shown in red. The O-linked sugar domain, the transmembrane domain and the cytoplasmic domain are indicated by a solid black line. The cell membrane is shown as a horizontal structure. At the cell surface the ectodomain of the LDLR is extended from the cell membrane and the LDLR binds LDL through its ligand-binding domain (left). At the acidic pH of the sorting endosome, LDL is released from the LDLR and the LDLR adopts a closed conformation whereby ligand-binding repeats 4 and 5 interact with the β-propeller (right). The figure is not drawn to scale.

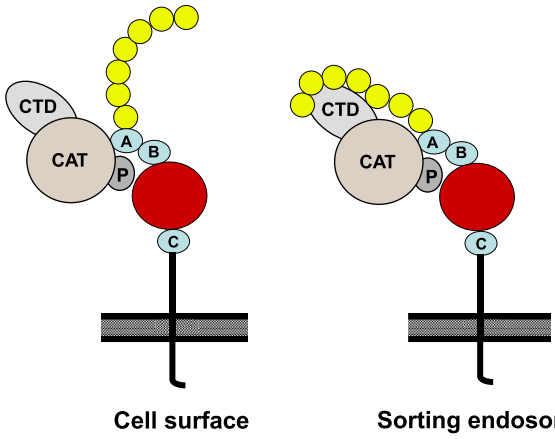

Fig. 2. PCSK9 prevents the LDLR from adopting a closed conformation in the sorting endosome. PCSK9 consisting of a prodomain (P), a catalytic domain (CAT) and a C-terminal domain (CTD) binds to the EGF-A repeat of the LDLR at the cell surface through its catalytic domain. At the acidic milieu of the sorting endosome, the C-terminal domain of PCSK9 obtains an increased positive charge and electrostatically attracts the negatively charged ligand-binding domain of the LDLR. This prevents the LDLR from adopting a closed conformation at acidic pH. The figure is not drawn to scale.

amino acids. The transmembrane domain has 22 amino acids and the cytoplasmic domain which contains the motifs required for concentrating the LDLR in clathrin-coated pits, has 50 amino acids.

LDL which binds to the ligand-binding domain at the cell surface, is released from the LDLR at the acidic pH of the sorting endosome [6] (Fig. 1). Released LDL is confined to the vesicular part of the sorting endosome which matures to become a late endosome [6]. LDL is finally degraded in the lysosome. Concomitant with the release of LDL in the sorting endosome, the LDLR folds back on itself to obtain a closed conformation whereby ligand-binding repeats 4 and 5 interact with the β-propeller [7] (Fig. 1). The LDLR then recycles back to the cell surface.

2. Proprotein convertase subtilisin/kexin type 9

Proprotein convertase subtilisin/kexin type 9 (PCSK9) has been shown to play a major role in regulating plasma LDL cholesterol levels through its ability to mediate intracellular degradation of the LDLR [8–10].

PCSK9 is a zymogen consisting of 692 amino acids of which residues 1–30 constitute the signal peptide [8]. The remainder of the protein is divided into three domains. The prodomain consists of residues 31–152, the catalytic domain consists of residues 153–454 and the cysteine- and histidine-rich C-terminal domain consists of residues 455–692 [11,12]. After intramolecular autocatalytic cleavage in the endoplasmic reticulum, the cleaved prodomain is non-covalently bound to the catalytic domain of the mature PCSK9 to block enzymatic activity and to act as a chaperone to promote proper folding and exit out of the endoplasmic reticulum [8]. In contrast to other proprotein convertases, PCSK9 does not undergo a second cleavage to release the prodomain [8]. PCSK9 is therefore secreted as an enzymatic inactive protein.

3. PCSK9-mediated degradation of the LDLR

At the cell surface, the catalytic domain of PCSK9 binds to the EGF-A repeat of the LDLR [9,13] (Fig. 2). The residues of the LDLR and PCSK9 involved in this interaction have been well characterized [9,13,14]. Following binding of PCSK9 to the LDLR at the cell surface, the LDLR:PCSK9 complex is internalized through clathrin-coated pits [9,15].

Whereas, LDL is released from the LDLR at the acidic milieu of the sorting endosome, the affinity of PCSK9 to bind to the LDLR increases 120–150 fold at acidic pH [11,12,16,17]. This makes PCSK9 remain bound to the LDLR in the sorting endosome and prevents the LDLR from adopting a closed conformation at acidic pH [18] (Fig. 2). There is a 1:1 stoichiometry between the LDLR and PCSK9. Thus, PCSK9 does not exhibit a general effect on the LDLRs within a clathrin-coated pit or within a sorting endosome, but rather acts as a tag to promote degradation of an individual LDLR. The question then is how an LDLR with bound PCSK9 is identified in the sorting endosome and rerouted to intracellular degradation.

4. Role of the cytoplasmic domain of the LDLR

For several receptors that are rerouted to intracellular degradation after having bound their ligands, such as the EGF receptor, ligand-binding introduces a conformational change of the cytoplasmic domain which leads to ubiquitination and activation of the endosomal sorting complex required for trafficking (ESCRT) machinery [19]. This machinery translocates these receptors to the vesicular part of the sorting endosome for transport down the endosomal/lysosomal tract. However, because an LDLR lacking the cytoplasmic domain also undergoes PCSK9-mediated degradation [20], modifications of the cytoplasmic domain or an interaction between the cytoplasmic domain and ubiquitin or adaptor proteins, are not involved in rerouting the LDLR with bound PCSK9 to intracellular degradation.

An alternative mechanism for intracellular degradation could involve an interaction within the endosomal lumen between a co-receptor on one hand and PCSK9 or the LDLR:PCSK9 complex on the other hand. This could lead to ubiquitination of the cytoplasmic domain of the co-receptor and activation of the ESCRT machinery. However, data from Wang et al. [15] showing that PCSK9 is able to degrade the LDLR when ubiquitination is inhibited or the ESCRT machinery is inactivated, exclude such a mechanism. Wang et al. [15] have also shown that the LDLR is degraded when proteasomal activity is inhibited or when the autophagocytic pathway is inactivated. Thus, PCSK9-mediated degradation of the LDLR does not

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