LRP1: A chameleon receptor of lung inflammation and repair

Lukasz Wujak[a], **Jennifer Schnieder**[a], **Liliana Schaefer**[b] and **Malgorzata Wygrecka**[a,c]

***a* - Department of Biochemistry,** *Justus Liebig University, Friedrichstrasse 24, 35392 Giessen, Germany*
***b* - Goethe University School of Medicine,** *University Hospital, Theodor-Stern Kai 7, 60590 Frankfurt am Main, Germany*
***c* - Member of the German Center for Lung Research (DZL),** *Germany*

Correspondence to Malgorzata Wygrecka: *at: Department of Biochemistry, Justus Liebig University, Friedrichstrasse 24, 35392 Giessen, Germany. malgorzata.wygrecka@innere.med.uni-giessen.de.*
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Abstract

The lung displays a remarkable capability to regenerate following injury. Considerable effort has been made thus far to understand the cardinal processes underpinning inflammation and reconstruction of lung tissue. However, the factors determining the resolution or persistence of inflammation and efficient wound healing or aberrant remodeling remain largely unknown. Low density lipoprotein receptor-related protein 1 (LRP1) is an endocytic/signaling cell surface receptor which controls cellular and molecular mechanisms driving the physiological and pathological inflammatory reactions and tissue remodeling in several organs. In this review, we will discuss the impact of LRP1 on the consecutive steps of the inflammatory response and its role in the balanced tissue repair and aberrant remodeling in the lung.

Introduction

Low density lipoprotein receptor-related protein (LRP) 1 is a ubiquitously expressed protein. High levels of LRP1 are found in the liver, brain and lung [1,2]. This multifunctional, endocytic receptor plays a role in numerous diseases such as hepatic steatosis, kidney fibrosis, acute respiratory distress syndrome (ARDS), Alzheimer's disease and atherosclerosis where it controls inflammation, tissue remodeling and clearance of extracellular molecules [3–8].

LRP1 is a member of the LDLR superfamily which furthermore includes the LDL-receptor, megalin, LRP1B, LRP3, LRP4, LRP5, LRP6, the very low density lipoprotein receptor (VLDLR) and the apolipoprotein E receptor 2 (apoER2) [9,10]. Structurally, LRP1 consists of the five domains described hereafter (Fig. 1). The extracellular domain of LRP1, also called the heavy α-chain (515 kDa), comprises four clusters (I–IV) of ligand-binding type cysteine-rich repeats which include 2, 8, 10, and 11 repeats, respectively [1]. More than 100 ligands of LRP1 are described, amongst them are matrix metalloproteinases (MMP), urokinase-type plasminogen activator (uPA), transforming growth factor (TGF)-β1 and apolipoprotein E [9,11]. Ligand-binding is mediated by clusters II and IV [12]. The clusters are separated by 1–4 epidermal growth factor (EGF) precursor homology domains. Structurally, two EGF repeats, followed by six YWTD repeats and one EGF repeat build one EGF precursor homology domain. In addition, six EGF repeats non-covalently conjugate the extracellular domain and the light β-chain (85 kDa) which consists of the single membrane-spanning segment and the cytoplasmic domain. The latter contains one YXXL motif and two NPXY motifs that regulate the functions of LRP1 [1,13]. The YXXL motif controls LRP1 endocytosis, whereas NPXY motifs serve as docking sites for cytoplasmic adaptor proteins, such as Shc, FE65 and mammalian Disabled1, which mediate LRP1-dependent signal transduction [14–16]. In order to recruit many adaptor proteins LRP1 has to be phosphorylated at the NPXY motifs [17]. As the phosphorylation status of LRP1 may be regulated by

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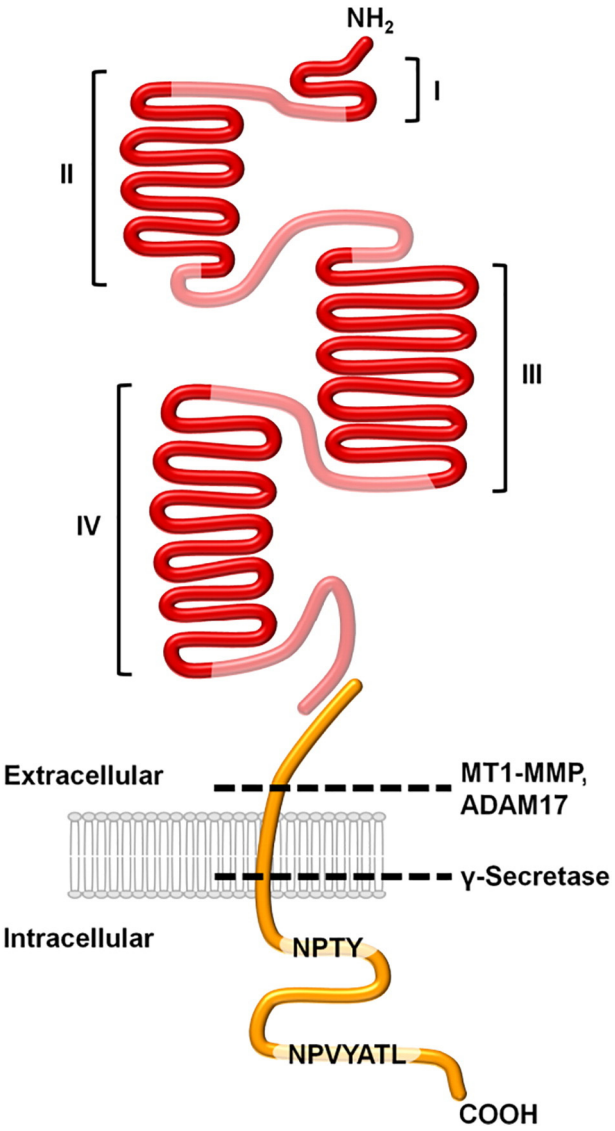

Fig. 1. Structure of LRP1. α- and β-chain are shown in red/pink and orange, respectively. Positions of ligand-binding clusters (I–IV, red) connected with epidermal growth factor precursor homology domains (pink) and locations of NPXY motifs (membrane-proximal NPTY motif and membrane-distal NPVY motif overlapping the YXXL domain, YATL) are indicated. Additionally, the sites of proteolytic cleavages mediated by MT1-MMP, ADAM17 and γ-Secretase are included.

a plethora of its own ligands, LRP1 exerts versatile functions in cellular responses, such as lipid and glucose metabolism, protein degradation, or signal transduction [18]. For example, in adipose tissue LRP1 plays a critical role in maintaining energy homeostasis [19]. In the liver, LRP1 mediates clearance of circulating cholesterol-rich remnant proteins [20] as well as proteases and inhibitor-protease complexes [21]. In the central nervous system, LRP1 controls neurotransmission [22] and blood-brain barrier permeability [23]. Besides, LRP1 protects the integrity of the vascular wall by modulating the PDGF signaling and deposition of extracellular matrix proteins [24] and it participates in the removal of cell debris and proper reepithelialization during wound healing [25]. The importance of LRP1 in physiological processes is highlighted by the fact that the disruption of the *Lrp1* gene in the mouse arrests the development of LRP1$^{-/-}$ embryos at the implantation stage [26].

In addition to these diverse physiological functions, several lines of evidence document the involvement of LRP1 in pathological inflammation and tissue repair. Herein, we review the findings demonstrating the function of LRP1 in inflammation and repair of the lung.

LRP1 as a modulator of the inflammatory response in the lung

Constant exposure of the pulmonary system to air pollutants and respiratory pathogens commands the need for effective, flexible and rapidly reacting defense mechanisms to combat the various insulting agents. An inflammatory reaction in the lung is an acute process which can be divided into several phases: initiation commenced by lung resident cells, recruitment of inflammatory cells and resolution [27]. The precise execution of this process is essential to clear the injuring factors from the lung. However, an ineffective removal of pathogens and endogenous irritants or an unsuccessful resolution may result in chronic inflammation and tissue remodeling. Therefore, the immune system has developed a number of tools to confront the harmful agents and a multitude of control systems ensuring the return to homeostasis [28]. In the following sections we will summarize the findings that associate LRP1 with the inflammatory response in the lung.

LRP1 initiates the inflammatory response in the lung

Resident alveolar macrophages (rAM) form the first line of defense against inhaled pathogens and other exogenous irritants or potentially dangerous host cellular debris in the respiratory system. The primary function of rAM is the uptake of bacteria and apoptotic or necrotic cells which may trigger the inflammatory reaction [29]. LRP1 is one of several cell surface receptors deployed by rAM to clear cellular debris. Hodge et al. [30] showed that the blockage of LRP1 reduces efferocytosis of apoptotic alveolar epithelial cells by rAM. The removal of apoptotic epithelial cells is an important protective mechanism and its dysregulation contributes to the

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