International Research Journal of Biochemistry and Bioinformatics Vol. 13(3) pp. 1-3, June, 2023
Available online http://www.interesjournals.org/IRJBB

Review Article

Low Density Lipoprotein Receptor-Related Protein

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Received: 02-Jun-2023, Manuscript No. IRJBB-23-103622; Editor assigned: 05-Jun-2023, PreQC No. IRJBB-23-103622 (PQ); Reviewed: 19-Jun-2023, QC No. IRJBB-23-103622; Revised: 23-Jun-2023, Manuscript No. IRJBB-23-103622 (R); Published: 30-Jun-2023, DOI: 10.14303/2250-9941.2023.63

Abstract

The protein known as cluster of differentiation 91 (CD91), also known as alpha-2-macroglobulin receptor (A2MR), apolipoprotein E receptor (APOER), or low density lipoprotein receptor-related protein 1 (LRP1), forms a receptor in the plasma membrane of cells that participate in receptor-mediated endocytosis. The LRP1 gene in humans encodes the LRP1 protein. As a crucial signalling protein, LRP1 is also involved in a number of biological functions, including lipoprotein metabolism and cell motility, as well as disorders including cancer, atherosclerosis, and neurodegenerative illnesses (Therese et al., 2019). LRP1, a member of the LDLR family, is widely expressed in a variety of tissues, although it is most prevalent in neurons, hepatocytes, and vascular smooth muscle cells (SMCs). LRP1 is involved in numerous cellular and biological processes, including lipid and lipoprotein metabolism, protease degradation, platelet derived growth factor receptor regulation, integrin maturation and recycling, regulation of vascular tone, regulation of blood brain barrier permeability, cell growth, migration, inflammation, and apoptosis, as well as diseases like neurodegenerative diseases, at the molecular level. To explain, LRP1 primarily contributes to the regulation of protein activity by binding target proteins as a co-receptor and transporting them to the lysosome for destruction together with integral membrane proteins or adaptor proteins like uPA (Yunusa et al., 2018).

INTRODUCTION

LRP1 or CD91 is a transmembrane receptor that has long been recognised for its function in lipoprotein endocytosis. But it is now understood that LRP1 is a multifunctional protein. As a scavenger receptor, LRP1 internalises a wide variety of extracellular ligands; as a regulatory receptor, it modulates cellular signalling in response to different extracellular stimuli; and as a scaffold receptor, LRP1 also has the capacity to collaborate with and control the activity of other membrane proteins like integrins and receptor tyrosine kinases (Celestina et al., 2021). LRP1 is able to connect the intracellular signalling and response with the extracellular surroundings thanks to these distinctive features. LRP1 is a widely distributed protein that is highly expressed upon damage in the heart, liver, brain, kidney, lung, and vasculatures. The lethality of LRP1 gene deletion, which stops mouse embryo development at an early stage, serves as a reminder of LRP1's significance. LRP1 plays a significant role in the pathogenesis of many disorders, including hepatic steatosis, renal fibrosis, acute respiratory distress syndrome (ARDS), Alzheimer's disease (AD), and atherosclerosis, thanks to its endocytic function and signalling capabilities. Additionally, recent studies have demonstrated that LRP1 is linked to the pathophysiological mechanisms behind AMI, IRI, and unfavourable LV remodelling (Ebeye et al., 2007). The LRP1 receptor has five structural domains and is a member of the LDLR superfamily. Furin-like endoproteases in the trans-Golgi compartment convert a 600-kDa precursor into the mature two-chain structure of LRP1. Four clusters of complement-like repeats (CCRs), which operate as ligand-binding sites, are spaced apart by epidermal growth factor (EGF) repeats in the 515-kDa -chain, which is fully extracellular. The cytoplasmic adaptor proteins Disabled-1, protein kinase (PKC), Shc, and FE65, which mediate LRP1-dependent signal transduction, dock at two NPxY motifs on the transmembrane 85-kDa chain, which is non-covalently conjugated to the former and contains the YxxL and dileucine motifs that serve as primary endocytosis signals. By directly ligand-binding or by transactivating signal pathways through its co-receptors, LRP1 starts signalling. Tyrosine phosphorylation at the NPxY

motifs is essential for LRP1-mediated signal transduction, even if the precise processes are only partially understood (Friday et al., 2015).

LRP1 interacts with more than 100 ligands, including as activated coagulation factors, growth factors, matrix proteins, proteinases, and proteinase-inhibitor complexes, as well as proteins involved in lipoprotein metabolism like apolipoprotein E (ApoE) and very low-density lipoprotein (VLDL). A large family of proteins known as serine proteinase inhibitors (SERPINs) interacts with target plasma proteinases to create complexes that control their concentration and activity. The resultant SERPIN-enzyme complexes (SECs) would eventually disintegrate, releasing the active enzymes into circulation, but they are chemically unstable (Ogori et al., 2016). The LRP1 protein, also known as the SEC receptor, can recognise the whole family of SERPINs, including 1-antitripsin (AAT), 2-macroglobulin (A2MG), and antithrombin III (ATIII), and it may also facilitate the endocytosis of these complexes for intracellular destruction. It's interesting to note that several ligands, like SERPINs and others bind to LRP1 and, acting as LRP1 agonists, have been demonstrated to increase LRP1 signalling, which controls a variety of biological processes in many organs, including the heart (Ashaye et al., 2006).

Myocardial cell death from acute myocardial infarction (AMI) is followed by a sterile inflammatory response that is an effort to remove cell debris and encourage heart healing. However, after an AMI, an excessive, unchecked, or unresolved inflammatory response results in more damage, poorer remodelling, and heart failure (HF). Therefore, further treatments are required to reduce the inflammatory response brought on by ischemia and reperfusion to stop long-term negative outcomes. The ubiquitous endocytic cell surface receptor known as low-density lipoprotein receptor-related protein 1 (LRP1) is capable of recognising a large variety of structurally and functionally varied ligands. Multiple intracellular signal pathways that LRP1 transduces control the inflammatory response, tissue remodelling, and cell survival following organ damage. Preclinical research has demonstrated a strong cardioprotective impact of non-selective and selective LRP1 agonists in the heart, lowering infarct size and cardiac dysfunction following AMI. LRP1 has the potential to be a new therapeutic target for AMI, according to findings from early phase clinical research using plasma-derived 1-antitrypsin (AAT), an endogenous LRP1 agonist, and SP16 peptide, a synthetic LRP1 agonist (Banjo et al., 2010). In this review, we will examine current findings linking LRP1 to cardiac inflammation and infarct healing as well as the cellular and molecular underpinnings of LRP1's roles in influencing the inflammatory reaction and the reparative process following damage in diverse peripheral tissues (Yusuf et al., 2017).

Acute myocardial infarction (AMI), despite treatment advancements, continues to be the most frequent cause of heart failure (HF) globally and is linked to an unacceptable high incidence of morbidity and death. The sudden destabilisation of a coronary atherosclerotic plaque with accompanying thrombosis that results in a protracted disruption of oxygen flow to the heart and subsequent myocardial cell death is a common cause of AMI. The development of primary percutaneous coronary intervention (PCI) and the enhancement of medical therapy fundamentally altered the course of AMI treatment and significantly enhanced prognosis. The extent of the infarct is reduced when coronary blood flow is quickly restored to the blocked artery ("time is muscle"), saving a significant portion of the at-risk myocardial. To estimate the ultimate infarct size owing to ischemia-reperfusion injury (IRI), however, the reperfusion of acutely ischemic myocardium causes myocardial damage on its own. IRI is a complicated, multifaceted process that involves both controlled and uncontrolled cell death, as well as a significant inflammatory response, neurohumoral activation, and oxidative stress. In the end, IRI causes paradoxical dysfunction of the cardiomyocytes and tissue damage while failing to save the entire viable ischemic myocardium. According to estimates, IRI-limiting measures in AMI might further shrink the infarct by 25%, maximising the advantages of reperfusion. This is crucial because the size of the infarct (initial damage) predicts the clinical outcome and 30% of patients who have had an AMI experience adverse structural and functional changes in the region surrounding the infarct as well as in the remote viable remote myocardium ("adverse left ventricular [LV] remodelling"), which have detrimental clinical and prognostic implications. A great deal of interest has been shown in understanding the pathophysiological mechanisms underlying IRI and its contribution to adverse LV remodelling over the past few decades, along with improving timing and technical reperfusion strategies and pharmacological neuro-hormonal blockade, leading to a large volume of experimental preclinical and clinical studies. The extent of the infarct, while being the most significant, is not the only factor that predicts increasing unfavourable LV remodelling, as has now become obvious. After an AMI, the structure and function of the ventricles gradually deteriorate. This is due to a complex interplay between the size of the infarct, exuberant acute and chronic persistent inflammation, increased wall stress, and neurohormonal activation (Ajiboso et al., 2012).

CONCLUSION

While the inflammatory reaction to injuries of any kind is an attempt to aid healing, it can also lead to further damage. Adverse cardiac remodelling and HF are brought on by the activation of an exacerbated inflammatory response in the heart after ischemia and non-ischemic damage. A widespread endocytic cell membrane receptor with the capacity to internalise a variety of structurally and functionally varied ligands is known as low-density lipoprotein receptor-related protein 1 (LRP1). Additionally, ligand- and cytotype-specific intracellular signalling pathways are activated when

particular ligands bind to LRP1, regulating the inflammatory response after organ damage and encouraging tissue repair and cell survival. In preclinical investigations, both non-selective and selective LRP1 agonists have been shown to activate LRP1-mediated signalling in the heart, which has a potent cardioprotective effect that reduces infarct size and cardiac dysfunction following AMI. The results of early phase clinical investigations using SP16 peptide, a synthetic LRP1 agonist, and plasma-derived 1-antitrypsin (AAT), an endogenous LRP1 agonist, are positive and imply that LRP1 modulation is safe. In order to lessen cardiac inflammatory damage, control infarct repair, and encourage cardiac recovery after AMI, activating LRP1-mediated signalling with both selective and non-specific LRP1 agonists may offer a unique therapeutic approach.

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