Biohelikon:Cell Biology (ISSN: 2348-3741), 2014 2:a12

Editorial/Review

# Low-density lipoprotein receptor-related protein 1 (LRP1) as a modulator of the vascular inflammatory response to modified LDL

**David de Gonzalo-Calvo [1] and Vicenta Llorente-Cortés [1*]**

[1] Cardiovascular Research Center, CSIC-ICCC, IIB-Sant Pau, Barcelona, Spain

[*] Corresponding author, Email: cllorente@csic-iccc.org

## Abstract

*Low density lipoprotein receptor-related protein 1* (LRP1) is a ubiquitously expressed cell surface receptor that mediates the internalization of more than 40 different ligands and participates in cell signaling. LRP1 plays a key pathophysiological role in the onset, development and thrombotic resolution of the atherosclerotic process due to its role in the intracellular lipid accumulation of vascular smooth muscle cells (VSMCs). During last years, LRP1 has also been proposed as a modulator of the inflammatory phenomenon in atherosclerosis. However, the investigations have obviated the function of LRP1 as a binding receptor of modified-lipids. In addition, the studies that analysed the relation between inflammation and LRP1 are focused on immunological cells from mice models. Whether LRP1 can respond to its modified-LDL ligands developing an inflammatory response in human VSMCs is unknown. Further investigations are, thus, necessary.

**Keywords**
Aggregated LDL; Atherosclerosis; Inflammation; LRP1.



*Low-density lipoprotein receptor-related protein-1* (LRP1) is an ubiquitously expressed and multifunctional membrane receptor involved in diverse biological processes, including lipoprotein metabolism, modulation of vascular and blood brain barrier integrity, activation of lysosomal enzymes and cell migration, among others [1]. LRP1 mediates the internalization of more than 40 different ligands and participates in intracellular signalling [1,2]. Alterations in receptor expression are associated with several pathological conditions such as Alzheimer's disease, cardiovascular disease or cancer [3,4].

Deregulation of vascular LRP1 expression is a key event in the etiology of atherosclerosis. LRP1 receptor is involved in the binding and internalization of matrix-retained aggregated LDL (agLDL), a major modification of LDL in the arterial intima, which leads to the intracellular lipid accumulation in vascular smooth muscle cells (VSMCs) [5,6]. This mechanism is fundamental for VSMCs to become foam cells, an essential step in the initiation and progression of atherosclerosis [7]. Additionally to its role in foam cell formation, LRP1 plays a central pathophysiological role in vascular remodeling [8] and prothrombotic transformation of the atheromatous plaque [9]. Indeed, agLDL uptake by LRP1 affects the expression and activation of tissue factor, principal activator of coagulation, and the secretion of microparticles enriched in tissue factor, situations associated with acute coronary syndrome and metabolic syndrome [9]. LRP1-mediated VSMCs-lipid loading contributes to the alterations in the elastogenic/elastolytic potential of human vascular cells reducing the tropoelastin synthesis and altering the structure and dynamics of elastin [10]. Moreover, the accumulation of cholesterol esters mediated by LRP1 increases the expression of precursor and mature forms of the proteolytic enzyme cathepsin S, linked to extracellular matrix degradation [10].

During last decade LRP1 has long been proposed as a modulator of the inflammatory phenomenon in atherosclerosis. Using a transgenic mice that specifically lacks macrophage LRP1, Overton and colleagues demonstrated that LRP1 deletion initiates a pro-inflammatory response through increased secretion of pro-inflammatory and pro-atherogenic mediators, such as TNF-α and MCP-1 [11]. They also found that macrophage LRP1 deletion increases MMP-9 expression and activity indicating that LRP1 is essential for vascular integrity. Additionally, inhibition of mice macrophage LRP1 impairs cell migration [12], down-regulates anti-inflammatory marker expression and enhances the response to classic inflammatory activation stimuli [13]. LRP1 affects inflammatory signaling directly, through the binding of extracellular messengers or intracellular signaling molecules, or indirectly through interaction of LRP1 with other transmembrane receptors or endocytosis of extracellular factors [14]. Zurhove and colleagues proposed that LRP1 limits the LPS-induced inflammatory response by interacting with the interferon regulatory transcription factor 3 (IRF-3) and inducing its nuclear export and proteosomal degradation in murine peritoneal

macrophages [15]. Macrophage LRP1 deficiency increases cell death and inflammation by impairing phosphorylated Akt activation [16]. Finally, Gaultier and colleagues reported that expression of complement components is increased in LRP1-deficient macrophages, isolated from mice [17]. They proposed that LRP1 supresses basal activity of nuclear factor kB (NF-kB) pathway by regulating TNF receptor 1 (TNFR1) cell surface level.

Attending to this previous evidence, LRP1 is a key inflammatory regulator in atherosclerosis. Nevertheless, additional approaches to better understand the relationship between LRP1, inflammation and atherosclerosis are necessary. It has been clearly demonstrated that the interaction between lipids and inflammation plays a relevant role in the atherosclerotic process [18-20]. Modified lipids act on diverse cell types to instigate inflammation and proatherogenic mechanisms [21]. Due to its properties in modified-LDL interaction and inflammatory signaling, LRP1 is the perfect candidate for the crosstalk between lipid metabolism and inflammation. However, the investigations have obviated the pathophysiological function of LRP1 as a binding receptor of modified-lipids. In addition, the studies that analysed the relation between inflammation and LRP1 are focused on immunological cells of animal models. Recently, our group has demonstrated that agLDL per se increased LRP1 expression in human monocyte-derived macrophages (HMDM) [22]. Furthermore, we have reported a direct association between LRP1 levels and inflammatory mediators secretion in human VSMCs in hypoxic conditions [23]. However, whether LRP1 can respond to its modified-LDL ligand by inflammatory signaling or alterations in the release of inflammatory factors in VSMCs is unknown. Since VSMCs are crucial for foam cell generation and its inflammatory function in human atheroma plaque has long been underestimated, further investigations are fundamental [24]. The presumed effect of agLDL-LRP1 interaction on the regulation of inflammatory mechanisms could bring knowledge for understanding the molecular basis of atherosclerosis and opens the door to possible therapies.

## Acknowledgements

This work was funded by FIS PI11/00747 from Instituto de Salud Carlos III, and cofinanced by the European Fund for Regional Development (E.F.R.D) and by Red de Investigación Cardiovascular (RD RD12/0042/0027). DdGC is financed by by Red Investigación Cardiovascular (RD RD12/0042/0027).

## References

1. Lillis AP, Van Duyn LB, Murphy-Ullrich JE, Strickland DK (2008). LDL receptor-related protein 1: unique tissue-specific functions revealed by selective gene knockout studies. *Physiol Rev*, 88(3): 887-918.
2. Dalli J, Norling LV, Montero-Melendez T, Federici Canova D, Lashin H, *et al.* (2014). Microparticle alpha-2-macroglobulin enhances pro-resolving responses and promotes survival in sepsis. *EMBO Mol Med*, 6(1): 27-42.
3. Gonias SL, Campana WM2 (2014). LDL receptor-related protein-1: a regulator of inflammation in atherosclerosis, cancer, and injury to the nervous system. *Am J Pathol*, 184(1): 18-27.
4. Sagare A, Deane R, Bell RD, Johnson B, Hamm K, *et al.* (2007). Clearance of amyloid-beta by circulating lipoprotein receptors. *Nat Med*, 13(9): 1029-1031.
5. Llorente-Cortés V, Martínez-González J, Badimon L (2000). LDL receptor-related protein mediates uptake of aggregated LDL in human vascular smooth muscle cells. *Arterioscler Thromb Vasc Biol*, 20(6): 1572-1579.
6. Llorente-Cortés V, Otero-Viñas M, Hurt-Camejo E, Martínez-González J, Badimon L (2002). Human coronary smooth muscle cells internalize versican-modified LDL through LDL receptor-related protein and LDL receptors. *Arterioscler Thromb Vasc Biol*, 22: 387-393..
7. Lacolley P, Regnault V, Nicoletti A, Li Z, Michel JB (2012). The vascular smooth muscle cell in arterial pathology: a cell that can take on multiple roles. *Cardiovasc Res*, 95: 194-204.
8. Otero-Viñas M, Llorente-Cortés V, Peña E, Padro T, Badimon L (2007). Aggregated low density lipoproteins decrease metalloproteinase-9 expression and activity in human coronary smooth muscle cells. *Atherosclerosis*, 194: 326-333.
9. Llorente-Cortés V, Otero-Viñas M, Camino-López S, Llampayas, O, and Badimon L (2004). Aggregated low-density lipoprotein uptake induces membrane tissue factor procoagulant activity and microparticle release in human vascular smooth muscle cells. *Circulation*, 110: 452-459.
10. Samouillan V, Dandurand J, Nasarre L, Badimon L, Lacabanne C, Llorente-Cortés V (2012). Lipid loading of human vascular smooth muscle cells induces changes in tropoelastin protein levels and physical structure. *Biophysical Journal*, 103: 532-540.
11. Overton CD, Yancey PG, Major AS, Linton MF, Fazio S (2007). Deletion of macrophage LDL receptor-related protein increases atherogenesis in the mouse. *Circ Res*, 100(5): 670-677.
12. Cao C, Lawrence DA, Li Y, Von Arnim CA, Herz J, *et al.* (2006). Endocytic receptor LRP together with tPA and PAI-1 coordinates Mac-1-dependent macrophage migration. *EMBO J*, 25(9): 1860-1870.
13. May P, Bock HH, Nofer JR (2013). Low density receptor-related protein 1 (LRP1) promotes anti-inflammatory phenotype in murine macrophages. *Cell Tissue Res*, 354(3): 887-889.
14. May P (2013). The low-density lipoprotein receptor-related protein 1 in inflammation. *Curr Opin Lipidol*, 24(2): 134-137.
15. Zurhove K, Nakajima C, Herz J, Bock HH, May P (2008). Gamma-secretase limits the inflammatory response through the processing of LRP1. *Sci Signal*, 1(47): ra15.
16. Yancey PG, Blakemore J, Ding L, Fan D, Overton CD, *et al.* (2010). Macrophage LRP-1 controls plaque cellularity by regulating efferocytosis and Akt activation. *Arterioscler Thromb Vasc Biol*, 30(4): 787-795.
17. Gaultier A, Arandjelovic S, Niessen S, Overton CD, Linton M F, Fazio S, Campana WM, Cravatt BF, Gonias SL (2008). Regulation of tumor necrosis factor receptor-1 and the IKK-NF-kappaB pathway by LDL receptor-related protein explains the antiinflammatory activity of this receptor. *Blood*, 111: 5316-5325.
18. de Jager SC, Pasterkamp G (2013). Crosstalk of lipids and inflammation in atherosclerosis: the PRO of PGRN? *Cardiovasc Res*, 100(1): 4-6.
19. Im SS, Yousef L, Blaschitz C, Liu JZ, Edwards RA, Young SG, Raffatellu M, Osborne TF (2011). Linking lipid metabolism to the innate immune response in macrophages through sterol regulatory element binding protein-1a. *Cell Metab*, 13: 540-549.
20. McGettrick AF, O'Neill LA (2013). How metabolism generates signals during innate immunity and inflammation. *J Biol Chem*, 288(32): 22893-22898.
21. Weber C1, Noels H (2011). Atherosclerosis: current pathogenesis and therapeutic options. *Nat Med*, 17(11): 1410-1422.
22. Costales P, Castellano J, Revuelta-Lopez E, Cal R, Aledo R, Llampayas O, *et al.* (2013). Lipopolysaccharide downregulates CD91/low-density lipoprotein receptor-related protein 1 expression through SREBP-1 overexpression in human macrophages. *Atherosclerosis*, 227: 79-88.
23. Revuelta-López E, Castellano J, Roura S, Gálvez-Monton C, Nasarre L (2013). Hypoxia induces metalloproteinase-9 activation and human vascular smooth muscle cell migration through low-density lipoprotein receptor-related protein 1-mediated pyk2 phosphorylation. *Arterioscler Thromb Vasc Biol*, 33: 2877-2887.
24. Allahverdian S, Pannu PS, Francis GA (2012). Contribution of monocyte-derived macrophages and smooth muscle cells to arterial foam cell formation. *Cardiovasc Res*, 95(2): 165-172.