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Lipocalin Family Proteins and Their Diverse Roles in Cardiovascular Disease

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Abstract

The lipocalin (LCN) family members, a group of small extracellular proteins with 160–180 amino acids in length, can be detected in all kingdoms of life from bacteria to human beings. They are characterized by low similarity of amino acid sequence but highly conserved tertiary structures with an eight-stranded antiparallel β-barrel which forms a cup-shaped ligand binding pocket. In addition to bind small hydrophobic ligands (i.e., fatty acids, odorants, retinoids, and steroids) and transport them to specific cells, lipocalins (LCNs) can interact with specific cell membrane receptors to activate their downstream signaling pathways, and with soluble macromolecules to form the complex. Consequently, lipocalins exhibit great functional diversity. Accumulating evidence has demonstrated that lipocalin family proteins exert multiple layers of function in the regulation of many physiological processes and human diseases (i.e., cancers, immune disorders, metabolic disease, neurological/psychiatric disorders, and cardiovascular disease). In this review, we firstly introduce the structural and sequence properties of lipocalins. Next, six lipocalins including apolipoprotein D (ApoD), ApoM, lipocalin 2 (LCN2), LCN10, retinol-binding protein 4 (RBP4), and Lipocalin-type prostaglandin D synthase (L-PGDS) which have been characterized so far are highlighted for their diagnostic/prognostic values and their potential effects on coronary artery disease and myocardial infarction injury. The roles of these 6 lipocalins in cardiac hypertrophy, heart failure, diabetes-induced cardiac disorder, and septic cardiomyopathy are also summarized. Finally, their therapeutic potential for cardiovascular disease is discussed in each section.

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Conflict of interest

All authors including H.-H. Yang, X. Wang, S. Li, Y. Liu, R. Akbar, and G.-C. Fan confirm that this article content has no conflict of interest.

Keywords

Lipocalin; Biomarker; Coronary artery disease; Myocardial infarction; Cardiac hypertrophy; Cardiomyopathy

1. Introduction

Lipocalins (LCNs), a group of typically small extracellular proteins with 160–180 amino acids in length, belong to the calycin superfamily that also includes other 4 families: acid-binding proteins (ABPs), avidins, triabins, and metalloproteinase inhibitors (MPIs) (Flower, North, & Attwood, 1993). The term “lipocalin” was initially proposed by Pervaiz & Brew in 1987 for a group of proteins including α1-microglobulin (A1M, also referred to as protein HC), human α1-acid glycoprotein (AGP), bovine β-lactoglobulin, and serum retinol-binding protein (RBP), which was based on their sequence homologies, disulfide bond pattern, and functional similarities in their ability to bind lipophilic molecules inside a cup-shaped protein fold (Pervaiz & Brew, 1987). Over the past decades, there are >1000 *LCN* genes identified among bacteria, plants, fungi, animals, and at least 20 *LCN*-like genes exist in the human genome (Charkoftaki, et al., 2019; Du, et al., 2015; Urzua, et al., 2006). Interestingly, lipocalin genes have a conserved arrangement of exons/introns with a primary pattern including 7 exons and 6 introns (C. Guo, et al., 2010; Hamil, et al., 2003; Suzuki, et al., 2006). They are usually organized into clusters at the same chromosome, which may be generated by functional divergence or duplications with evolutionary time (Hamil, et al., 2003; Suzuki, et al., 2004; Suzuki, et al., 2006). For example, human *LCN* genes are mostly detected in the Chromosome 9, and mouse *LCN*s are mostly clustered in chromosome 2 (Fig. 1). Furthermore, 18 of 20 human LCN genes have mouse orthologs (Table 1) which share a high degree of similarity (Charkoftaki, et al., 2019; Du, et al., 2015; Urzua, et al., 2006). Among all 20 *LCN* genes, LCN7 shows the highest percent similarity (90%), whereas *LCN*15 and *LCN*13 (*OBP2A*) display the lowest percent identity (39%) to their mouse orthologs (Table 1). Please note that *LCN*1 (also known as tear per-albumin or von Ebner’s gland protein) (Glasgow, et al., 1993; Holzfeind, Merschak, Wojnar, & Redl, 1997; Lassagne, Ressot, Mattei, & Gachon, 1993) and PAEP [progestagen-associated endometrial protein, also referred to as glycodelin (GD), a secreted immunosuppressive glycoprotein] (Joshi, Smith, & Stokes, 1980) are found only in human, whereas Lcn3, 4, 5 11, 16, 17 and all the functional major urinary protein genes (MUPs) exist only in mouse (Charkoftaki, et al., 2019). Human LCN6 gene is the orthologous gene of mouse Lcn5 (Hamil, et al., 2003).

LCNs were originally characterized to transport or store a range of small hydrophobic molecules such as odorants, retinol, steroid hormones, and various secondary metabolites (Flower, 1995, 1996; Flower, North, & Sansom, 2000). However, owing to their common molecular recognition patterns that include: 1) binding to specific cell membrane receptors, 2) high affinity to small hydrophobic molecules, and 3) the transient formation of complexes with soluble macromolecules, it is now becoming increasingly clear that lipocalins exert multiple layers of biological functions in the modulation of cell proliferation, differentiation, death, and ageing (Akerstrom, Flower, & Salier, 2000; Flower, 1995, 1996; Grzyb, Latowski, & Strzalka, 2006). They are also associated with the regulation

of immune response/inflammation, smell reception, reproduction, cancer development, metabolic disorders, and cardiovascular remodeling (Ganfornina, Akerstrom, & Sanchez, 2022; Redl & Habeler, 2022; Virtanen, 2021). As carrier proteins, LCNs could act in the general clearance of intracellular and extracellular hydrophobic molecules (Flower, 1996). Clinically, LCNs have been extensively explored as biochemical biomarkers for the diagnosis of human disease (Bacci, Cavallari, de Rozier-Alves, Alves Bda, & Fonseca, 2015; Bergwik, Kristiansson, Allhorn, Gram, & Akerstrom, 2021; Krol-Grzymala, et al., 2022; Sawyer, 2021; Sivalingam, et al., 2017; Steinhoff, Lass, & Schupp, 2021; Wong & Tse, 2021; Zabetian-Targhi, Mahmoudi, Rezaei, & Mahmoudi, 2015). In this review, we firstly introduce the structural and sequence properties of LCNs, and then summarize their diverse roles in coronary artery disease, cardiac vessel integrity, myocardial infarction, cardiac hypertrophy, and their associated heart failure. We also highlight both beneficial and detrimental effects of LCNs in diabetic and septic cardiomyopathy. Finally, their therapeutic potentials to the treatment of cardiovascular disease are discussed.

2. Characterization of Lipocalin Family Proteins

It is well recognized that the similarity of amino acid sequences among lipocalin family members is very low falling below 20% (Flower, et al., 2000). However, their three-dimensional structure is highly preserved with eight antiparallel β-strands (labelled A-H) forming a fold or calyx in a cylindrical manner with a “closed end” on one side and an “open end” on the opposite side (Flower, et al., 2000) (Fig. 2). The “open end” provides an access into the central cavity for the internal ligand-binding with and transporting small hydrophobic compounds including lipids, odorants (e.g., pheromones), retinoids, and steroid hormones (Flower, et al., 2000; Grzyb, et al., 2006; Schlehuber & Skerra, 2005). The eight β-strands, connected by seven loops (L1-L7), coil in a right-handed manner around a central axis and interact through transversal hydrogen bonds (Grzyb, et al., 2006). The first loop L1 is a large and flexible omega-type loop which functions as a dynamic lid for the “open end” of the β -barrel, and the other six are short hairpin-type loops (Flower, et al., 1993) (Fig. 2). Previous work has performed analysis for the conservation of amino acid sequence and structure within lipocalin proteins and identified that there is a common lipocalin fold characterized by three large structurally conserved regions (SCRs): SCR1 (strand A and its preceding 3_{10}-like helix), SCR2 (strands F and G, and their linking loop L6), and SCR3 (strand H and adjoining residues) (Flower, et al., 1993; Flower, et al., 2000) (Fig. 2). Despite the fact that other SCRs of the common core are identified, they are small and can be neglected. For example, one recent study by Du *et al* showed that human lipocalin proteins share four SCRs (Du, et al., 2015).

Notably, some LCNs contains three SRCs, whereas other LCNs have only one or two SCRs (Flower, et al., 2000). Accordingly, the LCN family can be divided in two groups: kernel LCNs and outlier LCNs. The Kernel lipocalins, representing a core set of LCNs, share three conserved sequence motifs corresponding to the three main SCRs of the lipocalin fold (Flower, et al., 2000; Grzyb, et al., 2006). The outlier LCNs typically share no more than two SCRs and are more diverse. Based on this categorization, A1M, ApoD, complement C8 gamma chain (C8γ), LCN2, lipocalin-type prostaglandin D2 synthase (L-PGDS), PEAP, RBP4, and all mouse MUPs belong to kernel lipocalins; while AGP1, AGP2, ApoM, LCN1,

LCN13, and LCN14 are included in the outlier category (Charkoftaki, et al., 2019; Du, et al., 2015; Flower, et al., 2000; Grzyb, et al., 2006). It is important to note here, among all apolipoproteins (ApoA, ApoB, ApoC, ApoD, ApoE, ApoF, ApoH ApoL, ApoM), both ApoD and ApoM share no amino acid sequence similarities with other apolipoproteins but < 20% homology with lipocalins and both contain distinct SCR motifs which ApoD protein has all three SCRs of LCN (kernel lipocalin), whereas ApoM protein contains one SCR only (outlier lipocalin) (Charkoftaki, et al., 2019; Du, et al., 2015).

Although lipocalin proteins are structurally highly conserved and similar, their binding ligands and receptors are divergent, leading to their functional different (Akerstrom, et al., 2000; Ganfornina, et al., 2022; Grzyb, et al., 2006; Redl & Habeler, 2022; Virtanen, 2021). For example, LCN1, one of four major proteins in human tears functions as a lipid sponge on the ocular surface (Glasgow, et al., 1993; Holzfeind, et al., 1997; Lassagne, et al., 1993). LCN2 can bind metalloproteinase 9 (MMP9), lipoprotein receptor-related protein 2 (LRP2), toll-like receptor 4 (TLR4), and 24p3R to mediate various inflammatory response (Guardado, Ojeda-Juarez, Kaul, & Nordgren, 2021; Jaberi, et al., 2021). LCN7 (also named tubulointerstitial nephritis antigen-like 1, TINAGL1) acts as a matricellular regulator of angiogenesis through activation of the TGF-β signaling pathway and increased secretion of VEGF (Brown, et al., 2010; L. Sun, Dong, Gu, Guo, & Yu, 2019). LCN13 and LCN14 may regulate glucose homeostasis (Buhler, et al., 2021; Cho, Zhou, Sheng, & Rui, 2011; Lee, et al., 2016; Zhou & Rui, 2013). In addition, LCNs could be internalized into cells, and transferred to lysosomes either for degradation [i.e., L-PGDS] or performing their function there (Mohri, et al., 2006; Nagata, et al., 2009). They can also interact with mitochondria in damaged cells (Kristiansson, et al., 2020; Olsson, et al., 2013). For example, Olsson *et al* previously showed that A1M could bind with high affinity to apoptotic cells and is localized to mitochondria through specifically binding to a subunit of Complex I (Olsson, et al., 2013). Furthermore, extracellular LCNs exist in diverse formats: bound to protein partners, lipoprotein particles, or membrane vesicles, which may yield varied effects (Redl & Habeler, 2022; Virtanen, 2021). As lipid-associated proteins, LCNs have been well studied in the regulation of metabolic diseases (see reviews elsewhere (Bacci, et al., 2015; Christoffersen, 2021; Frances, Tavernier, & Viguerie, 2021; Jaberi, et al., 2021; Nono Nankam & Bluher, 2021; Zabetian-Targhi, et al., 2015)). However, recent years have also witnessed the great progress made on the investigation of major LCNs (i.e., ApoD, ApoM, LCN2, LCN10, L-PGDS, and RBP4) in the field of cardiovascular diseases, as what we focus on below.

3. Lipocalins in Coronary Artery Disease and Myocardial Infarction

Coronary artery disease (CAD) is recognized to be the leading cause of death worldwide (Frak, et al., 2022; Hetherington & Totary-Jain, 2022; Schuett, Lehrke, Marx, & Burgmaier, 2015). The critical pathological change observed in CAD patients is atherosclerosis with the cholesterol and lipid-based blockage that usually causes chronic inflammation and myocardial infarction (Frak, et al., 2022; Hetherington & Totary-Jain, 2022; Schuett, et al., 2015). LCNs are secreted proteins and can be detected in the blood, urine, and other body fluids (Akerstrom, et al., 2000; Flower, 1995, 1996; Ganfornina, et al., 2022; Grzyb, et al., 2006; Redl & Habeler, 2022; Virtanen, 2021). Over past decades, therefore, tremendous effort has been made to define lipocalins as diagnostic and prognostic biomarkers for

atherosclerosis and ischemic heart disease. Currently, several LCN proteins (i.e., LCN2 and RBP4) have been identified as risk factors to promote atherosclerosis and myocardial injury (Cheng, et al., 2014; Dong, Li, & Tang, 2015; Hemdahl, et al., 2006; G. Huang, et al., 2012; F. Li, Xia, Li, & Yang, 2014; Lindberg, et al., 2012; Y. Liu, Wang, Chen, & Xia, 2015; Sahinarslan, et al., 2011; Shibata, et al., 2020; Sivalingam, et al., 2018; Soylu, et al., 2015; Wan, et al., 2014). By contrast, multiple LCNs (i.e., ApoD, ApoM, and L-PGDS) are found to have anti-atherogenic properties and protective effects against myocardial infarction injury (Ahnstrom, et al., 2008; Annema, et al., 2022; Hosbond, et al., 2014; Inoue, et al., 2008; Kurano & Yatomi, 2018; Sarjeant, et al., 2003; Su, Jiao, Yang, & Ye, 2009; H. Sun, et al., 2019; Tsukamoto, et al., 2013; X. Zhang, et al., 2021). Therefore, the following contents focus on the roles of LCN2, RBP4, ApoD, ApoM, and L-PGDS in CAD and ischemia heart disease.

3.1. Lipocalins serve as biomarkers for coronary artery disease and ischemic heart disease:

3.1.1. Apolipoprotein D (ApoD)—Apolipoprotein D (ApoD) is an atypical apolipoprotein with a structure like lipocalins and belongs to LCN family (Weech, et al., 1991). While it is a component of the high-density lipoprotein (HDL), its relative abundance in HDL particles is low (1–2%) (Rassart, Desmarais, Najyb, Bergeron, & Mounier, 2020). Nonetheless, the majority of circulating ApoD (~ 83%) is carried by HDL particles, while a small fraction is bound to low-density lipoproteins (LDLs) and very low-density lipoproteins (VLDLs) (Blanco-Vaca, Via, Yang, Massey, & Pownall, 1992; Rassart, et al., 2020; Soiland, et al., 2007; Weech, et al., 1991). Recently, increasing evidence has indicated that aberrant expression of ApoD is linked to the altered lipid metabolism and risk of CAD (Annema, et al., 2022; Sarjeant, et al., 2003; H. Sun, et al., 2019; Tsukamoto, et al., 2013; X. Zhang, et al., 2021). For example, Sun *et al* (2019) utilized iTRAQ labeling followed by 2D LC-MS/MS to compare the urinary proteome of CAD cohorts (n=22) to healthy controls (n=22) (H. Sun, et al., 2019). Their results revealed that urine ApoD levels were significantly lower in CAD patients than healthy cohorts. Further analysis showed that ApoD together with TFF1 (Trefoil Factor 1) could diagnose CAD with 85% sensitivity and 99% specificity. However, Tsukamoto *et al* (2013) (Tsukamoto, et al., 2013) reported that increased ApoD deposition is detectable in the atherosclerotic lesions of humans, and the plasma ApoD levels were markedly increased in an atherosclerotic mouse model (ApoE-KO). To clarify such a difference, a recent study by Zhang *et al* (2021) conducted a deep RNA-sequencing on whole blood collected from a cohort of CAD patients with early myocardial infarction (MI, n=55), high coronary artery calcification (CAC) without prior MI (n=72), and controls (n=71) (X. Zhang, et al., 2021). They observed that ApoD was significantly downregulated in all CAD patients with either early MI or high CAC, compared with controls. Controversially, Annema *et al* (2022) measured serum levels of ApoD in 531 Caucasian individuals who underwent coronary angiography (356 males and 175 females) and follow-up period over a median of 5.8 years (Annema, et al., 2022). These authors found that the higher cumulative incidence rates of mortality and adverse cardiovascular events is positively associated with the increased serum levels of ApoD. These data suggest that high levels of circulating ApoD could be a biomarker of poor prognosis in patients with suspected or established coronary artery disease. Collectively, it will be warranted

to investigate whether the elevation of serum ApoD levels in human patients may either contribute to CAD development or alternatively, implicate a compensatory mechanism or is an innocent bystander.

3.1.2. Apolipoprotein M (ApoM)—Apolipoprotein M (ApoM) was initially identified by Xu *et al* (1999) (N. Xu & Dahlback, 1999) as an apolipoprotein. However, later studies found that unlike most apolipoproteins, ApoM protein structure has a hydrophobic binding pocket resembling lipocalin proteins (Christoffersen, et al., 2006). ApoM is mainly synthesized in the liver and kidney, and to a minor extent, in adipose tissue (Christoffersen, et al., 2008; Sramkova, et al., 2019). While ApoM in the circulation is primarily carried by HDLs, it can bind to other lipoprotein subtypes including LDL, VLDLs, and chylomicrons (Christoffersen, et al., 2006; N. Xu & Dahlback, 1999). At present, numerous clinical investigations have focused on the role of ApoM in the prognosis of patients with coronary heart disease and myocardial infarction (Ahnstrom, et al., 2008; Kurano & Yatomi, 2018; Su, et al., 2009). Disappointingly, two earlier studies by Ahnström *et al* (2008) and Su *et al* (2009) suggest that plasma levels of apolipoprotein M are not associated with the risk of coronary artery disease (Ahnstrom, et al., 2008; Su, et al., 2009). However, Wolfrum *et al* (2005) found that silencing of ApoM expression in mice with small interfering RNA (siRNA) resulted in the accumulation of large (Wolfrum, Poy, & Stoffel, 2005), cholesterol-rich HDL particles, due to impaired conversion of HDL to pre-β-HDL, a subclass of lipid-poor apolipoproteins that serves as a key acceptor of peripheral cellular cholesterol (Wroblewska, 2011). This study suggests that reduced expression of ApoM may influence HDL and cholesterol metabolism and further affect the susceptibility to CAD. Along this line, the subsequent studies were shifted to explore single nucleotide polymorphisms (SNPs) of the proximal promoter region of ApoM gene in the whole blood of CAD patients (H. Guo, Zhao, Zhang, Chen, & Zhang, 2015; Jiao, et al., 2007; W. W. Xu, et al., 2008; P. H. Zhang, et al., 2016; Z. Zhang, Chu, & Yin, 2013; L. Zheng, et al., 2014; L. Zheng, et al., 2009). These SNPs may affect the transcription activity and expression levels of ApoM (H. Guo, et al., 2015; Jiao, et al., 2007; W. W. Xu, et al., 2008; P. H. Zhang, et al., 2016; Z. Zhang, et al., 2013; L. Zheng, et al., 2014; L. Zheng, et al., 2009). So far, at least 5 SNPs have been identified including T-1628G, C-1065A, T-855C, and T-778C, and C-724del that are linked to CAD and myocardial infarction (H. Guo, et al., 2015; Jiao, et al., 2007; W. W. Xu, et al., 2008; P. H. Zhang, et al., 2016; Z. Zhang, et al., 2013; L. Zheng, et al., 2014; L. Zheng, et al., 2009). For example, both Jiao *et al* (2007) and Zheng *et al* (2009) reported that there is a prominent association between the T-778C polymorphism and the risk of CAD in the Chinese population (Jiao, et al., 2007; L. Zheng, et al., 2009). Xu *et al* (2008) analyzed T-855C mutant allele in 418 CAD patients and 372 controls and showed that T-855C polymorphism carriers had an increased risk for CAD (W. W. Xu, et al., 2008). Accordingly, Zheng *et al* (2014) reported that occurrences of alleles T-1628G, T-855C and C-724del were significantly higher in CAD patients compared to non-CAD patients (L. Zheng, et al., 2014). They further confirmed that −855C and −724del could decrease ApoM expressions. These results were also validated by Zhang *et al* (2016) who showed that T-855C in the ApoM promoter could be a biomarker and provides binding sites for AP-2α, leading to a reduction of ApoM transcription activity (P. H. Zhang, et al., 2016).

Furthermore, Guo *et al* (2015) investigated the relationship between −724del in the ApoM promoter and myocardial infarction. They observed that the −724Del frequency in the MI group was significantly higher than that in the controls (H. Guo, et al., 2015), Accordingly, plasma ApoM levels were remarkably decreased but the total cholesterol (TC) levels were dramatically increased in MI patients with −724Del allele, in comparison to control samples. These results indicate that −724del polymorphism of ApoM promoter suppresses its transcription activity, leading to the downregulation of ApoM protein expression, and increased the risk of MI. Nonetheless, it remains unclear and needs to further determine whether other ApoM SNPs in addition to −724del could serve as a biomarker for ischemic heart disease.

3.1.3. Lipocalin 2 (LCN2)—LCN2 was initially identified from simian virus 40 (SV-40)–infected mouse kidney cells in 1989 by Hraba-Renevey *et al* (Hraba-Renevey, Turler, Kress, Salomon, & Weil, 1989) and later, the LCN2 protein was isolated from human neutrophil granules, and named neutrophil gelatinase-associated lipocalin (NGAL) (Kjeldsen, Johnsen, Sengelov, & Borregaard, 1993). At the present, LCN2 is defined as a pleiotropic glycoprotein that belongs to the lipocalin family (Charkoftaki, et al., 2019). In addition to secretion by activated neutrophils, LCN2 can be also released by multiple cell types including endothelial cells, macrophages, epithelial cells, kidney tubular cells and hepatocytes (Flo, et al., 2004). The expression of NGAL is dynamically altered in several acute and chronic pathological processes such as cell differentiation and proliferation, fibrosis, inflammation, iron trafficking, and metabolic disorders (Helanova, Spinar, & Parenica, 2014). NGAL has gained increasing attention as a potent early biomarker of renal injury, inflammation and more recently as a valuable biomarker of atherosclerosis and ischemic heart disease (Cheng, et al., 2014; Hemdahl, et al., 2006; Lindberg, et al., 2012; Sahinarslan, et al., 2011; Shibata, et al., 2020; Sivalingam, et al., 2018; Soylu, et al., 2015).

In the case of atherosclerotic arteries, numerous groups have reported that increased levels of serum or urinal LCN2 correlate with atherosclerosis risk factors, disease severity burden and mortality. For example, Ni *et al* (2013) measured serum LCN2 levels in a Chinese cohort of 261 in-patients who underwent coronary angiography (169 men and 92 postmenopausal women; CAD: 188 and non-CAD: 73). They observed that serum LCN2 levels were significantly higher in male patients than females and interestingly, significant differences or correlations were seen only in men with CAD, compared to non-CAD (Ni, et al., 2013).

Similarly, Lahiri *et al* (2018) reported that plasma LCN2 in patients admitted with acute coronary syndromes (ACS) can be considered as a possible new risk marker in ACS because it is able to predict hospital mortality (Lahiri, Alex, & George, 2018). Likewise, Soylu *et al* (2015) collected peripheral blood samples from 45 patients with normal coronary arteries (NCA) who underwent coronary angiography and 47 patients with non-ST elevation ACS (NSTE-ACS) (Soylu, et al., 2015). They observed that serum levels of LCN2 were remarkably higher in the NSTE-ACS group, in comparison to with the NCA control samples. Further analysis showed that higher levels of LCN2 were correlated well with the complexity of lesion and severity of CAD patients with NSTE-ACS. These results suggest that serum levels of LCN2 on admission are positively associated with the burden of atherosclerosis in ACS patients with NSTE.

In the case of patients with STEMI (ST segment elevation myocardial infarction), Kirbis *et al* (2015) prospectively measured admission and in-hospital urine LCN2 by investigating 61 consecutive STEMI patients after primary percutaneous coronary intervention. They found that urine LCN2 was elevated very early after STEMI, suggesting it might be a marker of high risk for acute heart failure in an individual patient (Kirbis, Gorenjak, & Sinkovic, 2015). Similarly, Lindberg *et al* (2012), Helanova *et al* (2015), Barbarash *et al* (2017), Li *et al* (2019) consistently demonstrated that higher LCN2 level in the blood of patients with STEMI is an independent predictor of mortality (Barbarash, et al., 2017; Helanova, et al., 2015; C. Li, et al., 2019; Lindberg, et al., 2012). Together, these clinical observations strongly implicate that LCN2 is a risk biomarker for CAD and IHD (ischemic heart disease).

3.1.4. Lipocalin-type prostaglandin D synthase (L-PGDS): L-PGDS was originally discovered by Clausen (1961) as a β-trace in human cerebrospinal fluid (Clausen, 1961), and later was found to be identical to human L-PGDS (Hoffmann, et al., 1993; Watanabe, Urade, Mader, Murphy, & Hayaishi, 1994). L-PGDS is unique in its bifunctional character as both an enzyme synthesizing prostaglandin D2 (PGD2) (Urade, Fujimoto, & Hayaishi, 1985) and a lipophilic ligand-carrier protein of the lipocalin family (Urade & Hayaishi, 2000b). The amino acid sequence of L-PGDS has the homology with the lipocalin family members and possesses a typical lipocalin fold of β-barrel (Urade & Hayaishi, 2000a). While L-PGDS was initially detected in the central nervous system and male genital organs of various mammals (Clausen, 1961), it is also distributed in myocardial cells, atrial endocardial cells, and smooth muscle cells of the arteriosclerotic intima (Urade & Hayaishi, 2000a, 2000b). Eguchi *et al* (1997) reported that L-PGDS is accumulated in the atherosclerotic plaque of coronary arteries with severe stenosis. They further measured the plasma levels of L-PGDS in human patients with stable angina and showed that the L-PGDS levels were significantly higher in the cardiac vein than in the coronary artery (Eguchi, et al., 1997). These results indicate that L-PGDS is present in the stenotic site of patients with stable angina and can be secreted from the myocardium into the coronary circulation.

Along this line, a multicenter cooperative study by Inoue *et al* (2008) measured serum levels in a large cohort of 1013 consecutive patients with stable CAD and 241 controls (Inoue, et al., 2008). Their results indicated that the L-PGDS levels in CAD patients were significantly lower than controls. Multiple regression analysis further revealed that the L-PGDS level was the most powerful independent predictor of the coronary severity score. This study suggests that the reduced L-PGDS levels are related to the severity of CAD, and the measurement of serum L-PGDS levels can be helpful for screening of stable CAD prior to coronary angiography. Hosbond *et al* (2014) reported that L-PGDS is not a biomarker of atherosclerotic manifestations (Hosbond, et al., 2014), however, this investigation is based on a single blood test from a small cohort of 30 patients with ACS which appears to be less valuable.

3.1.5. Retinol binding protein 4 (RBP4)—The RBP4 was initially discovered by Quadro *et al* (1999) as an adipokine that binds specifically to vitamin A (retinol) and delivering it from the liver to target tissues and is therefore regulating circulating levels of vitamin A (Quadro, et al., 1999). RBP4 is produced mainly by the liver and adipose tissue

(Christou, Tselepis, & Kiortsis, 2012). Accordingly, RBP4 has been well characterized to involve the development of obesity and insulin resistance (Christou, et al., 2012). RBP4 has been proposed to involve in the pathophysiology of CAD, but accumulated findings on the association of RBP4 levels with CAD are inconsistent and even opposite, as reviewed below.

An earlier clinical investigation by Mallat *et al* (2009) demonstrated that serum level of RBP4 does not provide added value for predicting CAD risk beyond traditional risk factors (Mallat, et al., 2009). Subsequently, Sun *et al* (2013) determined plasma levels of full-length and several C-terminally truncated subfractions of RBP4 among 468 women who developed CHD and 472 matched controls in the Nurses' Health Study cohort (Q. Sun, et al., 2013). They observed that higher circulating full-length and total RBP4 levels but not truncated RBP4 are significantly associated with increased risk of woman patients with CHD in a time-dependent fashion. Consistently, a later study by Liu *et al* (2015) who also measured the plasma levels of RBP4 in 447 women (246 with ACS and 201 with stable CAD), and plasma levels of RBP4 were remarkably higher in stable CAD patients with complex coronary lesions than in those with simple lesions (Y. Liu, et al., 2015). Further multiple logistic regression analysis indicated that higher levels of RBP4 independently correlated with a 23% higher risk for complex lesions, and total plasma levels of RBP4 were predictors of cardiac death in female patients.

Regardless gender, *Calo* et al (2014) investigated the relationship between RBP4 levels and the presence and severity of CAD (Calo, Maiolino, Pagnin, Vertolli, & Davis, 2014), Lambadiari *et al* (2014), Li *et al* (2014), Perumalsamy *et al* (2021), Qian *et al* (2022), and Nar *et al* (2021) determined the relationship between RBP4 levels and the presence/severity of CAD. All these studies consistently observed that serum levels of RBP4 were greatly elevated in CAD patients compared to non-CAD cohorts, and independently correlated with CAD severity and adverse cardiovascular outcomes (Lambadiari, et al., 2014; F. Li, Xia, Li, et al., 2014; Nar, Sanlialp, & Nar, 2021; Perumalsamy, Ahmad, & Huri, 2021; Qian, Yan, Xu, Fang, & Ma, 2022).

Controversially, Wang *et al* (2018) investigated the role of RBP4 and the possible correlation between RBP4 levels and sex hormones, especially testosterone and estradiol, in CAD patients (n = 440) and healthy controls (n = 218) (H. Wang, et al., 2018). They observed that serum levels of RBP4 were significantly lower in male CAD patients, especially those with acute MI (myocardial infarction), than in control samples. However, there was no significant difference in serum RBP4 levels in female CAD patients between both groups. In addition, these authors found that RBP4 levels positively correlated with testosterone in male CAD patients (r = 0.124, p< 0.05). Logistic regression analysis revealed that RBP4 is a protective factor for CAD. Finally, they conclude that serum levels of RBP4 are significantly decreased and positively related with testosterone in men with CAD. Higher levels of RBP4 correlate well with lower risk of CAD. These results indicate that RBP4 could play a potential protective role for male but not for female CAD patients, which is totally opposite with other groups' findings, mentioned above.

Taken together, numerous epidemiological studies have investigated the correlation of serum RBP4 levels with the risk of CAD over the past years. Most studies have revealed similar

findings that elevated serum RBP4 levels are positively related to CAD (Calo, et al., 2014; Lambadiari, et al., 2014; F. Li, Xia, Li, et al., 2014; Y. Liu, et al., 2015; Mallat, et al., 2009; Nar, et al., 2021; Perumalsamy, et al., 2021; Qian, et al., 2022; Q. Sun, et al., 2013), whereas a nonsignificant or even negative correlations between RBP4 levels and CAD have also documented in other studies (Cubedo, et al., 2014; T. Liu, et al., 2019; Pan, et al., 2020; H. Wang, et al., 2018). Therefore, further studies will be performed to discern whether RBP4 levels really correlate with the risk of CAD, using a large cohort of CAD patients from multiple center and different races/populations.

3.2 Protective effects of ApoD, ApoM and L-PGDS against CAD and MI

As mentioned above, ApoD, a member of lipocalin family, plays a critical role in transporting lipids and other small hydrophobic molecules for metabolism (Sanchez & Ganfornina, 2021). Given that majority of circulating ApoD is bound with HDL, and dyslipidemia with increased LDL/ triglyceride and decreased HDL levels often predisposes an individual at risk to CAD (Sanchez & Ganfornina, 2021), ApoD therefore should have a great impact on the pathogenesis of CAD and its related myocardial infarction injury. In this regard, an earlier study by Sarjeant *et al* (2003) investigated whether ApoD could affect vascular smooth muscle cell (VSMC) proliferation, a critical culprit for atherosclerosis and arterial restenosis after angioplasty (Sarjeant, et al., 2003). They firstly observed that ApoD is accumulated in human atheromatous plaque but not in normal coronary arteries, suggesting the regulatory effect of ApoD on VSMCs during atherosclerosis. Further experimental results revealed that intracellular accumulation of ApoD can selectively inhibit PDGF-BB–induced VSMC proliferation by preventing translocation of phospho-ERK1/2 to the nucleus. These data suggest that an increased ApoD deposition in atherosclerotic lesions could be ascribed to a compensatory response of ApoD to help cholesterol removal from peripheral cells or derive from the consequence of defects in ApoD-mediated cholesterol trafficking (Sarjeant, et al., 2003). Indeed, Tsukamoto *et al* (2013) utilized a double-knockout mouse model (dKO) with homozygous null mutations in the HDL receptor (SR-BI) and apolipoprotein E (ApoE) genes which spontaneously develops occlusive, atherosclerotic CAD and ischemic heart failure (Tsukamoto, et al., 2013). They observed that the expression of ApoD in the dKO hearts was dramatically upregulated by 80-fold at the age of 43 days, compared with control mouse hearts. Interestingly, in mouse ischemic hearts, the expression of ApoD was substantially upregulated in non-infarcted but not in infarcted tissue at 48 h post-MI (Tsukamoto, et al., 2013). Considering that ApoD was previously shown to protect against hypertoxic stress in flies and mice and to be activated by neuronal injury (Sanchez & Ganfornina, 2021), therefore, Tsukamoto *et al* (2013) hypothesized that elevation of ApoD may be a protective mechanism of cardiac cells (cardiomyocytes, endothelia cells, *etc.*) in response to vessel occlusion and consequent ischemic stress (Tsukamoto, et al., 2013). Using ApoD-overexpressing and ApoD-KO mice, these authors clearly identified ApoD as a powerful protector against myocardial infarction injury (Tsukamoto, et al., 2013). Collectively, the mechanism underlying ApoD-mediated cardio-protection against ischemia injury is associated with: 1) a reduced atherosclerosis by disrupting p-ERK nuclear translocation; 2) an increased cell viability in cardiomyocytes and vessel endothelia cells (ECs), possibly due to the properly folded conformation of ApoD and

its antioxidant activity, 3) increased internalization of plasma-derived ApoD, and/or (4) a regulation of cell differentiation related to the angiogenic response (Fig. 3).

Like ApoD, circulating ApoM also binds to HDL particles. Earlier studies showed that ApoM-bound HDL had atheroprotective effects against LDL-oxidation *via* stimulating cholesterol efflux from macrophages and regulating pre-beta HDL formation (Christoffersen, et al., 2008; Christoffersen, et al., 2006; Sramkova, et al., 2019; Wolfrum, et al., 2005). However, a later study by Christoffersen *et al* (2011) discovered that ApoM could function as a chaperon to the bioactive sphingolipid, sphingosine-1-phosphate (S1P), with ~70% of S1P bound to ApoM (Christoffersen, et al., 2011). Further experimental results from other groups indicate that the complex of HDL-ApoM/S1P is able to connect HDL with endothelial cells to maintain an intact endothelial barrier and limit endothelial inflammation and apoptosis (Y. Liu & Tie, 2019; Ruiz, Frej, et al., 2017; Ruiz, Okada, & Dahlback, 2017). So far, several studies have showed that ApoM and S1P individually provide anti-atherogenic potential (Elsoe, et al., 2012; X. S. Huang, Zhao, Hu, & Luo, 2007; Wolfrum, et al., 2005). However, high levels of either ApoM or S1P could be associated with dyslipidemia (Hajny, Borup, Elsoe, & Christoffersen, 2021). In this regard, there are some discrepancies about the understanding of the ApoM/S1P-mediated protection against atherogenesis. For example, overexpression of ApoM in LDL-R-deficiency mice demonstrated protective effects against atherosclerosis (Christoffersen, et al., 2008; Sramkova, et al., 2019; Wolfrum, et al., 2005). However, such ApoM-mediated favorable consequence on atherosclerosis was only displayed in mouse models with unchanged LDL-cholesterol in comparsion to controls (Christoffersen, et al., 2008). Otherwise, elevation of ApoM levels caused even accelerated atherosclerosis (Christoffersen, 2021). The mechanism underlying such opposite results is unclear, but the impact of ApoM on the circulating LDL/VLDL particles and the lipoprotein lipase activity may play a role. Regarding S1P, overexpression of S1P showed beneficial to suppress or retard the progression of atherosclerosis in animal models through reduced macrophage apoptosis (Feuerborn, et al., 2017), but super-physiological concentrations of S1P displayed in SGLT2-knockout mice could induce dyslipidemia (Bektas, et al., 2010) which would have a potential harmful consequence on the cardiovascular system. Using ApoM-transgenic mice in which plasma levels of S1P are elevated by 3-fold, Morel et al (2016) showed that elevation of ApoM/S1P significantly reduced myocardial infarction injury by phosphorylating the gap junction protein connexin 43, and short-term treatment with S1P has a therapeutic potential in the fight against myocardial infarction damage (Morel, et al., 2016). Collectively, the complex of ApoM/S1P may have either beneficial or harmful consequence on the cardiovascular system. Therefore, it will be greatly needed for more investigations to understand the interplay between these molecules.

Unlike ApoD and ApoM as HDL-binding proteins, L-PGDS is the only member of LCN family characterized as an enzyme involved in the synthesis of Prostaglandin D2 (PGD_2), a molecule that involves in the regulation of many patho-physiological functions (Urade, 2021). In addition, L-PGDS binds retinoids, thyroids, amyloid β (Aβ) peptides, and diverse types of lipophilic ligands (Hoffmann, et al., 1993; Urade, et al., 1985; Urade & Hayaishi, 2000a, 2000b; Watanabe, et al., 1994). Currently, it is well documented that L-PGDS has neuro-protective effects against damage following either acute or chronic neurological

disorders (Hoffmann, et al., 1993; Urade, et al., 1985; Urade & Hayaishi, 2000a, 2000b; Watanabe, et al., 1994). Nonetheless, accumulating evidence has implicated that L-PGDS is highly expressed in the heart including in cardiomyocytes (Eguchi, et al., 1997; Han, et al., 2009; Katsumata, et al., 2014; Otsuki, et al., 2003; Tokudome, et al., 2009). Importantly, Tokudome *et al* (2009) reported that glucocorticoid-mediated protection during myocardial ischemia/reperfusion (I/R) is largely ascribed to the activation of L-PGDS-derived PGD_2 biosynthesis in cardiomyocytes (Tokudome, et al., 2009). Consistently, Katsumata *et al* (2014) showed that PGD_2 protects heart against I/R injury by activating Nrf2 predominantly *via* PGF(2α) receptor (Katsumata, et al., 2014). While reduced L-PGDS levels may contribute to the severity of CAD, it remains unclear whether elevation of L-PGDS is beneficial for the treatment of CAD. In addition, future studies will be needed to explore whether L-PGDS has a therapeutic value in ischemic heart disease.

3.3 Detrimental effects of LCN2 and RBP4 in CAD and MI.

LCN2 was initially identified as a protein isolated from specific neutrophil granules released at sites of infection and inflammation in human and was validated to be covalently bound with neutrophil gelatinase (Kjeldsen, et al., 1993). LCN2 has bacteriostatic properties through its sequestering iron from bacterial siderophores (Holmes, Paulsene, Jide, Ratledge, & Strong, 2005; Nairz, et al., 2009). In the case of atherosclerotic arteries, LCN2 may play a key role in vascular remodeling, because LCN2 can form a complex with MMP-9 and thereby, prevent MMP-9 degradation and reinforces its proteolytic activity contributing to the formation of an unstable atherosclerotic plaque (Hemdahl, et al., 2006). Indeed, the complex of LCN2/MM9 has been detected in atherosclerotic plaques and its concentration is increased in plaques with intramural hematoma and central necrosis (Cruz, Gaiao, Maisel, Ronco, & Devarajan, 2012; Hemdahl, et al., 2006; Leclercq, et al., 2007; te Boekhorst, et al., 2011). Recently, to evaluate the functional role of Lcn2 in different stages of atherosclerosis, Amersfoort *et al* (2018) generated a double knockout mouse model in which the expression of low-density lipoprotein receptor (LDLR) and Lcn2 are deficient (Amersfoort, et al., 2018). They showed that the contribution of Lcn2 to experimental atherosclerosis is stage-dependent as it appears to limit lesion development, whereas it potentially involves plaque instability at more advanced stages of atherosclerosis. In the case of ischemic heart disease, Sung *et al* (2017) observed that myocardial Lcn2 was significantly upregulated in mouse ischemic hearts, compared to sham-group (Sung, et al., 2017). Accordingly, both Lcn2-KO mice displayed less cardiac ischemic injury than WT mice. Furthermore, treatment with recombinant Lcn2 protein promoted ischemia-induced cardiac cell death and myocardial dysfunction through inhibiting the protective autophagic response to ischemia. Consistently, Xu *et al* (2012) showed that LCN2 could induce cardiomyocyte apoptosis by increasing intracellular iron accumulation (G. Xu, et al., 2012). In addition, Song *et al* (2018) showed that holo-Lcn2 (Lcn2-siderophore-iron, 1:3:1) promotes mitochondrial ROS generation and suppresses mitochondrial oxidative phosphorylation in the cultured adult rat cardiomyocytes, which may contribute to ischemia-triggered cardiac damage (Song, et al., 2018). Put all together, these data suggest that Lcn2 may play a detrimental role in the pathogenesis of coronary artery disease and ischemic heart disease.

Regarding RBP4, while it is well appreciated as a plasma transport protein for delivering retinol from liver to the tissues, it may have harmful effects in the pathophysiology of CAD and myocardial infarction injury, as summarized in Figure 4. For example, Li *et al* (2014) treated rat aortic smooth muscle cells (RASMCs) with different doses of RBP4 (1 and 4 μg/mL) and observed that RBP4 stimulated aberrant VSMC proliferation and migration *via* activation of the MAPK pathway, which may contribute to the formation of atherosclerotic plaques *in vivo* (F. Li, Xia, Sheikh, et al., 2014). Moreover, Liu *et al* (2017) reported that increased levels of RBP4 in aortic atherosclerotic lesions of both human and mice could promote the formation of macrophage-derived foam cells through the activation of scavenger-receptor CD36-mediated cholesterol uptake *via* the Toll-like receptor 4, but not retinol, thus accelerating the progression of atherosclerosis (Y. Liu, et al., 2017). Lastly, RBP4 can play important role in the regulation of endothelial inflammatory response and mitochondrial dysfunction, both of which greatly accelerate or influence atherogenesis in the coronary artery (J. Wang, et al., 2015). As for the detrimental role of RBP4 in ischemic heart disease, Zhang *et al* (2021) recently showed that RBP4 was significantly increased both *in vivo* ischemic mouse hearts and *in vitro* hypoxic cardiomyocytes (K. Z. Zhang, et al., 2021). These authors further found that the elevation of RBP4 may activate cardiomyocyte pyroptosis upon acute myocardial infarction, evidenced by that overexpression of RBP4 greatly stimulated LRP3 inflammasome and Caspase-1 activities and thereby, promoting gasdermin-D (GSDMD)-mediated pyroptosis. Using co-immunoprecipitation assay, the same authors identified that RBP4 bound directly with NLRP3 in cardiomyocytes. What's more, silencing of RBP4 in mouse hearts significantly reduced infarct size, limited AMI-induced pyroptosis and myocardial depression, in comparison to control samples. Taken together, these observations clearly indicate that RBP4 is a harmful factor by promoting cardiomyocyte pyroptosis *via* interaction with NLRP3 in the ischemic heart.

4. Lipocalins in Cardiac Hypertrophy and Heart Failure

Pathological cardiac hypertrophy occurs usually in response to hypertension, increased workload, or chronic stress, which finally leads to heart failure and is the single most important risk factor for cardiovascular death (Frieler & Mortensen, 2015). Among human lipocalin proteins, two members including RBP4 and LCN2 have been well characterized to positively regulate pathological cardiac remodeling and heart failure, as summarized below.

Solini *et al* (2009) observed that serum RBP4 levels are elevated in patients with hypertension without metabolic syndrome (Solini, Santini, Madec, Rossi, & Muscelli, 2009). Consistently, Kraus *et al* (2015) utilized animal model and showed that elevation of serum RBP4 levels raises blood pressure (BP), whereas Lowering RBP4 reduces BP through enhanced eNOS-mediated vasodilatation (Kraus, et al., 2015). These studies suggest that RBP4 may play a direct role in the regulation of BP and involve pressure overload-induced cardiac hypertrophy. Moreover, Gao *et al* (2016) also observed that circulating levels of RBP4 and adipose expression of RBP4 are significantly increased in cardiac hypertrophic mice induced by transverse aortic constriction and angiotensin-II (Ang-II) infusion, compared to controls (Gao, et al., 2016). Importantly, treatment of neonatal cardiomyocyte with RBP4 greatly increased myocyte size and enhanced protein synthesis together with elevated expression of hypertrophic markers by activating TLR4/MyD88-

mediated inflammatory pathways. Supportively, *Rbp4*-knockout mice are protected from Ang-II-induced cardiac hypertrophy (Kraus, et al., 2015).

Recently, Marques *et al* (2017) utilized genetic and environmental experimental mouse models to assess the association of LCN2 with concentric cardiac hypertrophy and its relation to the normal variation of human heart size and cardiac hypertrophy in diabetes mellitus (Marques, et al., 2017). They clearly demonstrated that higher levels of LCN2 are well correlated with cardiac hypertrophy, whereas adult Lcn2-knockout mice display significantly smaller hearts than wild-type controls. In human studies, higher *LCN2* expression was also found to correlate well with cardiac hypertrophy in healthy individuals and in patients with type 2 diabetes mellitus. The further in vitro studies by Marques *et al* revealed that overexpression of *Lcn2* in neonatal cardiomyocytes activates hypertrophic pathways, causing an increase in cardiomyocyte size but a decrease in their proliferation (Marques, et al., 2017). Collectively, this study suggests that Lcn2 is able to positively regulate cardiac hypertrophy. In support of these findings, Kim *et al* (2018) investigated the association between plasma levels of LCN2 and cardiac hypertrophy in patients with chronic kidney disease (CKD). They showed that higher plasma levels of LCN2 were independent predictors of cardiac hypertrophy and heart failure in patients with pre-dialysis CKD (Kim, et al., 2018).

More recently, Del Gaudio *et al* (2021) reported that loss of ApoM and loss of S1P transporter, Spns2, both can exaggerate cardiac hypertrophy in hypertension (Del Gaudio, et al., 2021), suggesting a protective role of ApoM/S1P signaling in hypertension and pathological cardiac hypertrophy. As for other lipocalin family members, while the expression levels of cardiac LCN6 and LCN10 in human patients with end-stage heart failure have been detected to be significantly lower than healthy controls (di Salvo, et al., 2015), their possible roles in cardiac hypertrophy are very limited.

5. Lipocalins in Diabetes-Induced Cardiac Dysfunction

Patients with diabetes have an increased risk of developing cardiovascular remodeling (Gustafsson, et al., 2004). Diabetes-induced heart failure (also termed as diabetic cardiomyopathy, DCM) occurs usually in the absence of other cardiac risk factors *e.g.* coronary artery disease, hypertension, or congenital heart diseases (Y. Zheng, Ley, & Hu, 2018). Over the past decades, a variety of mediators/factors including insufficient myocardial angiogenesis, cardiac fibrosis, cell death, lipid accumulation, inflammation, and oxidative stress have been defined as contributors to DCM (Jia, Hill, & Sowers, 2018). In this regard, lipocalin family members are well recognized to regulate lipid metabolism, insulin sensitivity, inflammatory response, oxidative stress, and angiogenesis, which are expected to play fundamental role in diabetic cardiomyopathy. However, the effects of lipocalins on the heart during diabetes have relatively less been studied. For example, LCN2 is a proinflammatory adipokine which is significantly elevated in the patients with obesity and diabetes (Y. Wang, et al., 2007) and clinical studies have also observed that there is a strong positive correlation between circulating LCN2 and heart failure (Chan, Sung, & Sweeney, 2015). Nonetheless, it remains unclear whether elevation of LCN2 directly contribute to diabetic cardiomyopathy.

Recently, we observed that the expression of Lcn2 is remarkably increased, whereas the Lcn10 expression is significantly downregulated in macrophages under metabolic stress conditions (Q. Li, et al., 2022). Accordingly, using a global knockout mouse model, we showed that ablation of Lcn10 could exacerbate diabetes-induced cardiomyopathy by skewing macrophages towards a pro-inflammatory phenotype and increased cardiac inflammatory response (Q. Li, et al., 2022). Mechanistically, we identified that Lcn10 deficiency in macrophages largely prevented Nr4a1 translocation to nuclei and disrupted its anti-inflammatory signaling pathway (Q. Li, et al., 2022). Our study suggests that reduction of Lcn10 may contribute to diabetes-induced cardiac dysfunction. Future investigations would be needed to elucidate whether elevation of Lcn10 expression/activity in macrophages or directly administration of recombinant Lcn10 protein has therapeutic potential for the treatment of diabetes-induced low-grade inflammation and concomitant cardiomyopathy. In addition, it will be warranted to explore whether other lipocalin family members are involved in diabetes cardiomyopathy.

6. Lipocalins in Sepsis-Induced Cardiomyopathy

Sepsis is a life-threatening syndrome due to multi-organ dysfunction induced by a dysregulated immune response to infection (Rudd, et al., 2020). Importantly, myocardial depression has been elucidated to be a major culprit to the increased risk of mortality and morbidity in patients with severe sepsis (Lin, et al., 2022). Although decades of intensive study, the precise mechanisms underlying sepsis-triggered immune dysregulation and cardiac dysfunction remain obscure (Beesley, et al., 2018; Carbone, Liberale, Preda, Schindler, & Montecucco, 2022; Hollenberg & Singer, 2021). As mentioned above, lipocalin family proteins have demonstrated diverse properties in the regulation of oxidative stress, immune response, vascular permeability, and cell survival, all of which are associated with sepsis. Therefore, in this regard, lipocalins may play good, bad, or ugly roles in the modulation of sepsis-triggered cardiomyopathy, which are discussed below.

Among human lipocalin family members, LCN2 is well characterized to serves as the potential biomarker in the assessment of severity and prediction of prognosis of patients with sepsis (Bagshaw, et al., 2010; Lentini, de Cal, Clementi, D'Angelo, & Ronco, 2012; Martensson, et al., 2010). In addition, Wang *et al* (2017) and Liu *et al* (2022) both observed that high plasma LCN2 correlates with high mortality and myocardial dysfunction in severe sepsis and septic shock (W. Liu, et al., 2022; B. Wang, et al., 2017). These clinical investigations suggest that increased levels of Lcn2 may have harmful effects and contribute to the pathogenesis of sepsis. However, an earlier study by Flo *et al*. (2004) demonstrated that exogenous Lcn2 directly inhibited the growth of *Escherichia coli* (E. coli) *via* its binding specificity for siderophores (Flo, et al., 2004). Furthermore, the presence or administration of Lcn2 protected against oxidative stress through upregulation of antioxidant enzymes (e.g., superoxide dismutase, heme oxygenase 1) *in vivo* during sepsis (Srinivasan, et al., 2012; Zhao, Wei, & Xu, 2015). Indeed, numerous studies have suggested that Lcn2 protects from organ failure in sepsis models (H. Li, et al., 2018; Srinivasan, et al., 2012; Wu, et al., 2010; Zhao, et al., 2015). Accordingly, Lcn2-null mice exhibited an increase in the bacterial burden and exacerbated sepsis (Bellmann-Weiler, et al., 2013; Z. Liu, Petersen, & Devireddy, 2013; Nairz, et al., 2015; Toyonaga, et al., 2016; Warszawska, et

al., 2013). Therefore, in view of all these data, it could be hypothesized that Lcn2 offers therapeutic promise against sepsis-induced myocardial cardiomyopathy. Controversially, a recent study by Huang *et al* (2022) showed that LCN2 deficiency led to the improvement of cardiac function in bacterial endotoxin (LPS)-induced septic mice through the inhibition of ferroptosis in cardiomyocytes (Y. Huang, et al., 2022). The *in vitro* studies further revealed that Lcn2 induced cardiomyocyte ferroptosis by increasing intracellular labile iron pool (LIP) via interacting with its receptor 24p3R on the surface of myocytes. Another study by Liu *et al* (2022) indicated that LCN-2 may involve in the process of septic cardiomyopathy through stimulating lipid accumulation and mitochondrial dysfunction (W. Liu, et al., 2022). Therefore, future studies with directly injection of recombinant Lcn2 protein into bacterial sepsis model rather than endotoxin-induced sepsis model are warranted to discern whether Lcn2 may harness host immune system to protect against sepsis-induced heart failure or Lcn2 may cause cardiomyocyte ferroptosis and lipid toxicity, leading to septic myocardial injury (Fig. 5).

Recently, Wang *et al* (2021) explored whether circulating Lcn10 serves as a prognostic tool in septic patients with myocardial depression (L. Wang, et al., 2021). They demonstrated that higher levels of serum LCN10 in septic patients are well correlated with the incidence of cardiac depression triggered by sepsis. Importantly, LCN10 appears a more reliable for the prediction of 28-day mortality than other biomarkers used clinically (L. Wang, et al., 2021). Using Lcn10-KO mouse model, we elucidated that loss of Lcn10 significantly promoted sepsis-induced cardiac dysfunction through increasing vascular leakage (Zhao H, 2023). By contrast, both endogenous and exogenous elevation of Lcn10 significantly reduced endothelial permeability and improved cardiac function during sepsis (Zhao H, 2023). Our results suggest that injection of recombinant Lcn10 protein could have therapeutic effects against sepsis-caused cardiomyopathy and mortality.

Unlike increased circulating LCN2 and LCN10 in septic patients, Kumaraswamy *et al* (2012) and Frej *et al* (2016) observed that the plasma levels of ApoM were significantly reduced in patients with severe sepsis (Kumaraswamy, Linder, Akesson, & Dahlback, 2012) (Frej, et al., 2016). As a carrier of S1P in HDL for endothelial barrier protection (Christoffersen, et al., 2011; Y. Li, et al., 2020), the decreased ApoM could contribute to the increased vascular leakage observed in sepsis. Indeed, Fan *et al* (2020) reported that the plasma levels of HDL/S1P were significantly decreased and negatively correlated with endothelial damage in sepsis, both in the animal model and in the septic patients (Fan, et al., 2020). The i*n vivo* HDL/S1P injection significantly reduced lung oedema and endothelial leakage in septic rats (Fan, et al., 2020). In addition, Kurano *et al* (2018) showed that ApoM protected mice from LPS-induced organ injury and death (Kurano, et al., 2018). Therefore, it will be very interesting to examine whether elevation of either ApoM or S1P has therapeutic potential for the improvement of sepsis-induced cardiac dysfunction and survival. As for the role of other lipocalin family members in sepsis-induced myocardial depression, there is very limited information in the literature.

7. Summary and Future Perspectives

Lipocalin family proteins, albeit the very low similarity of their amino acid sequences (< 20%), share a common three-dimensional structure (named lipocalin-fold) consisting of an eight-stranded antiparallel β -barrel (Charkoftaki, et al., 2019; Du, et al., 2015; Flower, et al., 1993; Pervaiz & Brew, 1987). They are not only important carriers of preferentially hydrophobic molecules, but also bind other ligands (i.e., siderophores, intact proteins) and membrane receptors (Akerstrom, et al., 2000; Flower, 1995, 1996; Flower, et al., 2000; Ganfornina, et al., 2022; Grzyb, et al., 2006; Redl & Habeler, 2022; Virtanen, 2021). Furthermore, they can internalize in cells and traffic to intracellular organelles (i.e., mitochondria, lysosomes) and nuclei (Asimakopoulou, et al., 2017; Kurozumi, et al., 2020; Yammine, Zablocki, Baron, Terzi, & Gallazzini, 2019). Consequently, they exert diverse biological and physiological effects (i.e., behavior, chemo-sensation, development, and reproduction) and are involved in a variety of pathological processes in many human diseases such as cancers, immune disorders, metabolic disease, neurological/psychiatric disorders, and cardiovascular disease. This review presents a detailed summary of major lipocalins in cardiovascular diseases which have been investigated so far. Since lipocalins are mainly extracellular proteins that can be detected in the blood, urine, and other body fluids, therefore, numerous studies have focused on the identification of lipocalins as biomarkers for the diagnosis and prognosis of cardiovascular diseases. In this review, we center on 6 major lipocalins including ApoD, ApoM, LCN2, LCN10, RBP4, and L-PGDS, and heavily summarize their diagnostic/prognostic values and their potential effects on coronary artery disease and myocardial infarction injury. We also highlight the roles of these 6 lipocalins in cardiac hypertrophy and heart failure as well as diabetic cardiomyopathy and sepsis-induced myocardial depression. Their possible therapeutic strategies for the treatment of cardiovascular diseases are also discussed in each section.

Currently, the large number of lipocalins have been identified to date. However, the individual pathophysiological function and its underlying mechanisms remains largely unclear. In particular, the knowledge about lipocalin receptors, cellular uptake of lipocalins, and the related signaling pathways is still limited. In this regard, future studies will be greatly needed to elucidate whether lipocalins interact with the distinctive or common receptor on cardiovascular cells, and which lipocalin could be used to develop pharmaceutical drug for cardiovascular disease. It is important to note here that human lipocalins have been chosen as appropriate scaffolds for protein engineering to generate anticalin drugs, because lipocalin-fold has highly structural plasticity of their binding sites which can be modified to specifically recognize and tightly bind disease-related molecular targets (Achatz, Jarasch, & Skerra, 2022; Schiefner, Gebauer, Richter, & Skerra, 2018; Schiefner & Skerra, 2015; Skerra, 2008). Anticalin proteins are usually generated by combinatorial design based on natural lipocalins which contain a densely central β-barrel supporting four structurally variable loops that form a binding pocket (Rothe & Skerra, 2018). Accordingly, reshaping of this variable loop region could yield a different anticalin protein (lipocalin isotype) with distinct ligand specificities or physiological functions. Initial application of these anticalin proteins was driven by the discovery of some structural similarity between their binding sites and those of immunoglobulins (antibodies)

(Schlehuber & Skerra, 2005). The first LCN1-derived anticalin protein was developed for therapeutically targeting human VEGF-A, a key factor of tumor angiogenesis and ocular disease (Ferrara & Kerbel, 2005). The human LCN2 has been proved particularly successful for the design of binding proteins with novel specificities and so far, more than 20 Lcn2-based anticalins have been generated towards different medically relevant target proteins, mainly in the areas of cancer and inflammatory diseases [see reviews elsewhere (Achatz, et al., 2022; Deuschle, Ilyukhina, & Skerra, 2021)]. Indeed, anticalin proteins can be produced by modified human lipocalins with specificities for prescribed targets of interest, ranging from small molecules to proteins/peptides. The affinities of the resulting anticalin proteins can be competitive for or even better than those accessible by antibody technology. Furthermore, anticalin proteins comprise a single polypeptide chain that folds into a stable eight-stranded β-barrel with exposed N- and C-terminals (neither of which is part of the binding pocket) which makes them ideal building blocks to generate multi-valent, multi-paratopic and multi-specific proteins, thus offering novel therapeutic modalities for human diseases. Most importantly, anticalin proteins have low immunogenic potential, as they are modified from soluble human lipocalins that are enriched in plasma or other body fluids and only a limited number of amino acids are altered from their natural counterparts. All these advantages of anticalin proteins mentioned above make them attractive as therapeutics for cardiovascular disease. Therefore, it will be worthy to spend effort on developing such anticalin drugs aiming at cardiovascular disorders by selecting suitable targets, and then designing and modifying human lipocalins.

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List of Abbreviations

A1M	α1-microglobulin
Aβ	amyloid β
ABPs	acid-binding proteins
ACS	acute coronary syndromes
AGP	α1-acid glycoprotein
ApoD	apolipoprotein D
ApoM	apolipoprotein M
BP	blood pressure
C8γ	complement C8 gamma chain
CAC	coronary artery calcification
CAD	Coronary artery disease

CKD	chronic kidney disease
dKO	double-knockout mouse model
ECs	endothelia cells
GD	glycodelin
GSDMD	gasdermin-D
HDL	high-density lipoprotein
LCNs	Lipocalins
LCN2	Lipocalin 2
LDLs	low-density lipoproteins
LDLR	low-density lipoprotein receptor
LIP	labile iron pool
L-PGDS	lipocalin-type prostaglandin D2 synthase
LPS	lipopolysaccharide
LRP2	lipoprotein receptor-related protein 2
MMP9	metalloproteinase 9
MUPs	major urinary protein genes
MPIs	metalloproteinase inhibitors
NCA	normal coronary arteries
NGAL	neutrophil gelatinase-associated lipocalin
NSTE-ACS	non-ST elevation ACS
PAEP	progestagen-associated endometrial protein
PGD2	prostaglandin D2
RASMCs	rat aortic smooth muscle cells
RBP4	retinol binding protein 4
ROS	reactive oxygen species
SCRs	structurally conserved regions
SNPs	single nucleotide polymorphisms
STEMI	ST segment elevation myocardial infarction
TC	total cholesterol

TINAGL1	tubulointerstitial nephritis antigen-like 1
TLR4	toll-like receptor 4
VLDLs	very low-density lipoproteins
VSMC	vascular smooth muscle cell

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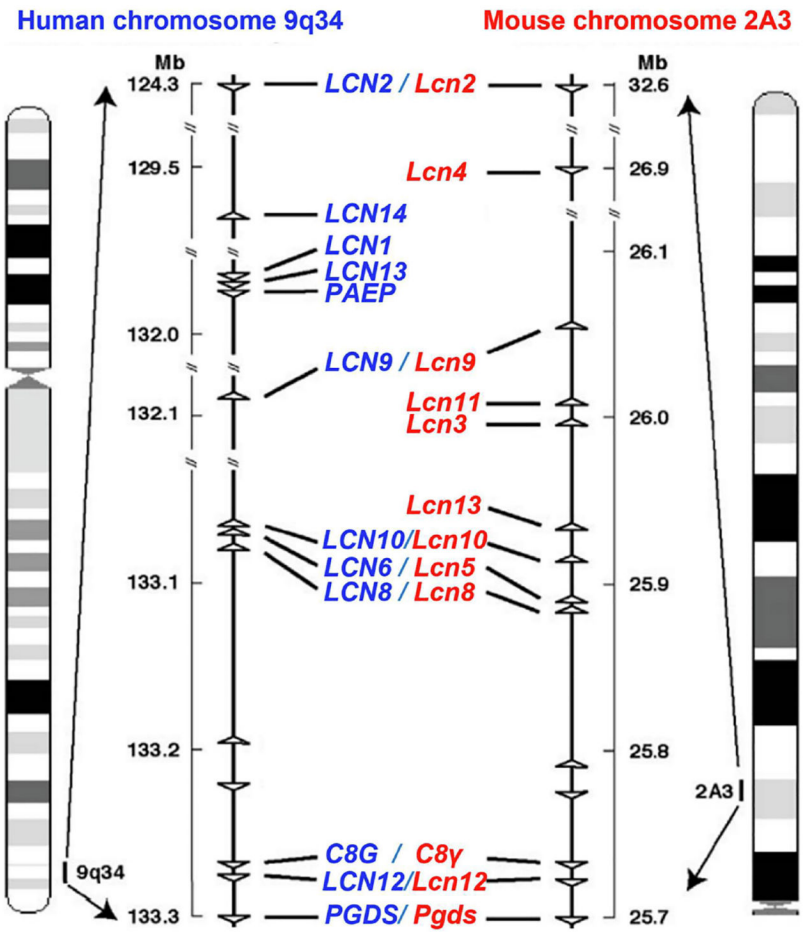

Figure 1: A lipocalin gene cluster located at the mouse chromosome 2 and the human chromosome 9.

Syntonically homologous cluster of lipocalin genes at the chromosomes is conserved between human and mouse. Each triangle symbol represents gene locus and gene orientation. Adapted from Suzuki et al. (2004).

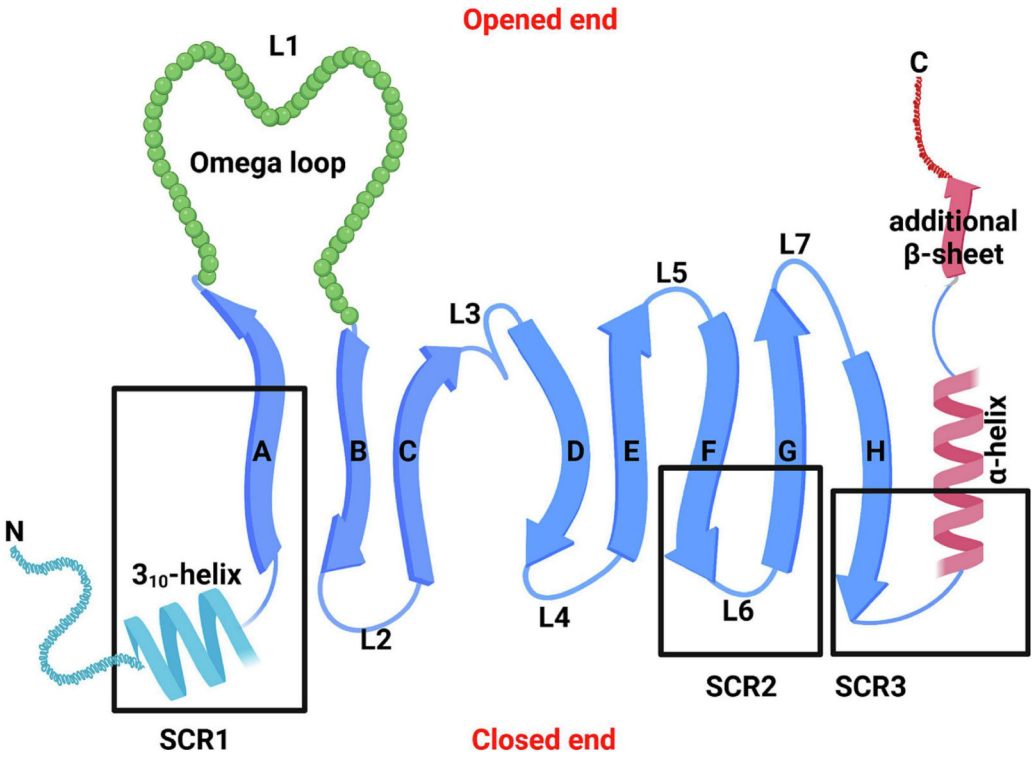

Figure 2: Structure of the lipocalin fold.

The eight β-strands of the antiparallel β-sheet plus one additional β-strand at the C-terminal are shown as arrows and marked A-H. The N-terminal 310 like helix and C-terminal α-helix are also marked. Connection loops are labelled L1-L7. There are four loops (L1, L3, L5, and L7) located at one end of the lipocalin L-barrel which open for the internal ligand-binding site. In parallel, there are three L-hairpin loops (L2, L4 and L6) at the other end and the N-terminal polypeptide chain crosses this end of the barrel to link strand A through a conserved 3^{10} helix to close this end of the barrel. The three structurally conserved regions (SCRs) of the lipocalin fold (SCR1, SCR2, and SCR3) are labelled as heavy boxes. Adapted from Flower et al. (2000).

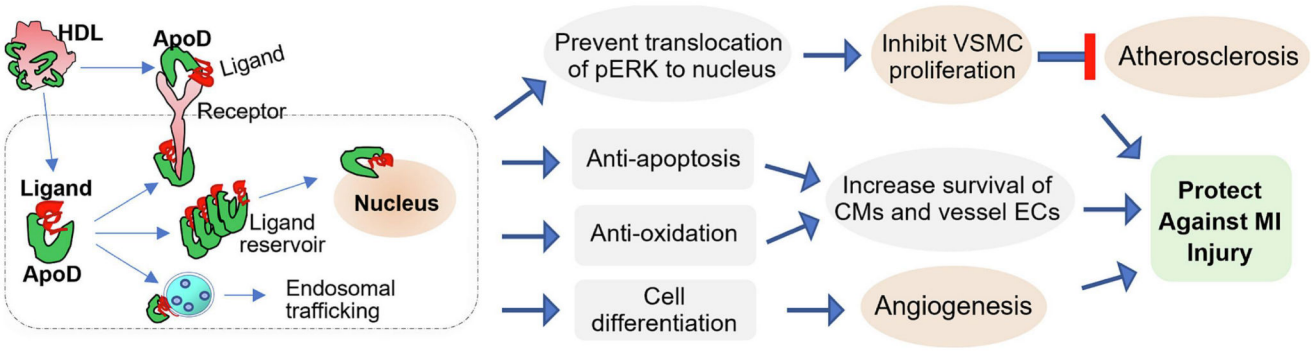

Figure 3: ApoD-mediated protection against atherosclerosis and myocardial infarction (MI) injury.

Circulating ApoD can be internalized into the cell in which ApoD binds hydrophobic ligands, while may pile up as an intracellular reservoir to stimulate the effect on gene transcription of nuclear receptor ligands or prevent ligand translocation to the nucleus. ApoD is also able to exert endosomal trafficking of its bound ligands/proteins. In addition, ApoD can interact with transmembrane receptors and complex with other proteins either inside or outside the cell. Accordingly, ApoD has been identified to prevent pERK translocation to the nucleus, leading to the inhibition of aberrant VSMC proliferation and thereby, attenuation of atherosclerosis. Moreover, increased ApoD levels can protect cardiomyocytes (CMs) and vessel endothelial cells (ECs) against apoptosis and oxidation as well as promote cell differentiation-related angiogenesis, leading to reduced myocardial infarction (MI) injury.

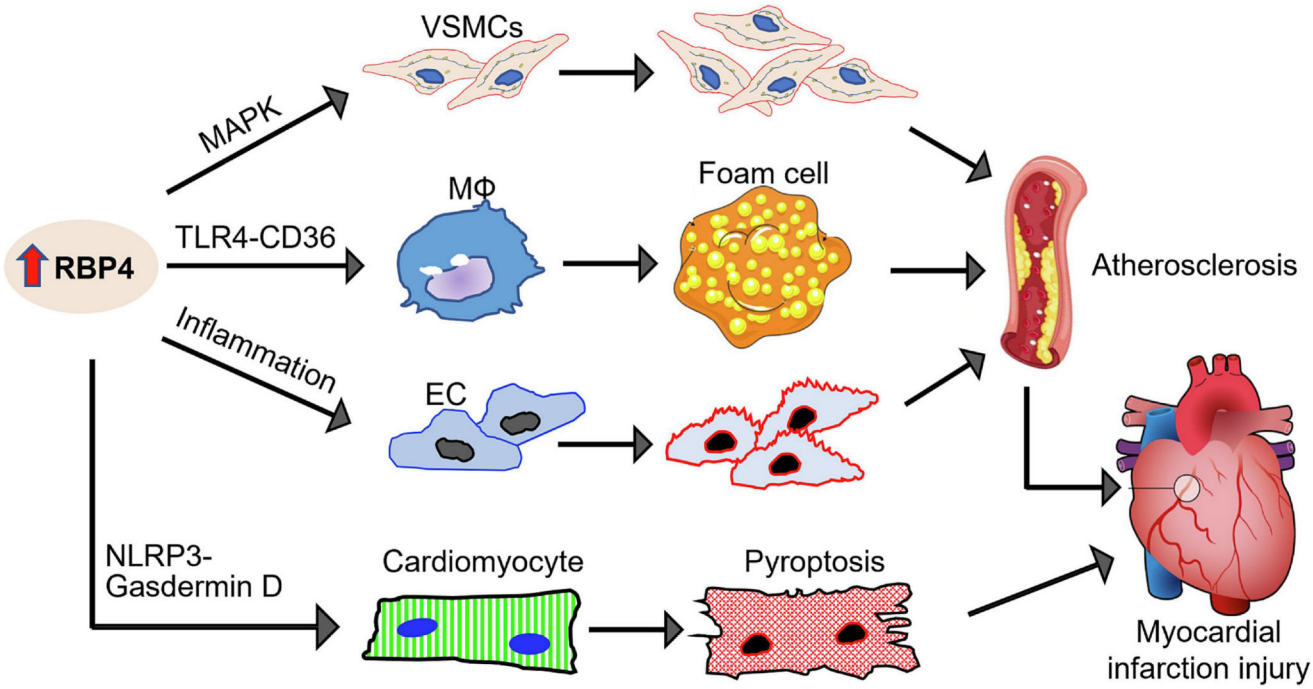

Figure 4: RBP4-mediated harmful effects on atherosclerosis and myocardial infarction (MI) injury.

Elevation of RBP4 can: 1) activate MAPK pathway and promote aberrant VSMC proliferation; 2) interact with TLR4 and activate CD36-mediated cholesterol uptake in macrophages (MΦs) which form foam cells; 3) increase mitochondrial dysfunction and inflammation in endothelial cells (ECs). All these significantly accelerate atherogenesis. In addition, elevation of RBP4 can interact directly with NLRP3 in cardiomyocytes, leading to GSDMD (gasdermin-D)-dependent pyroptosis and thereby, aggravate myocardial infarction injury.

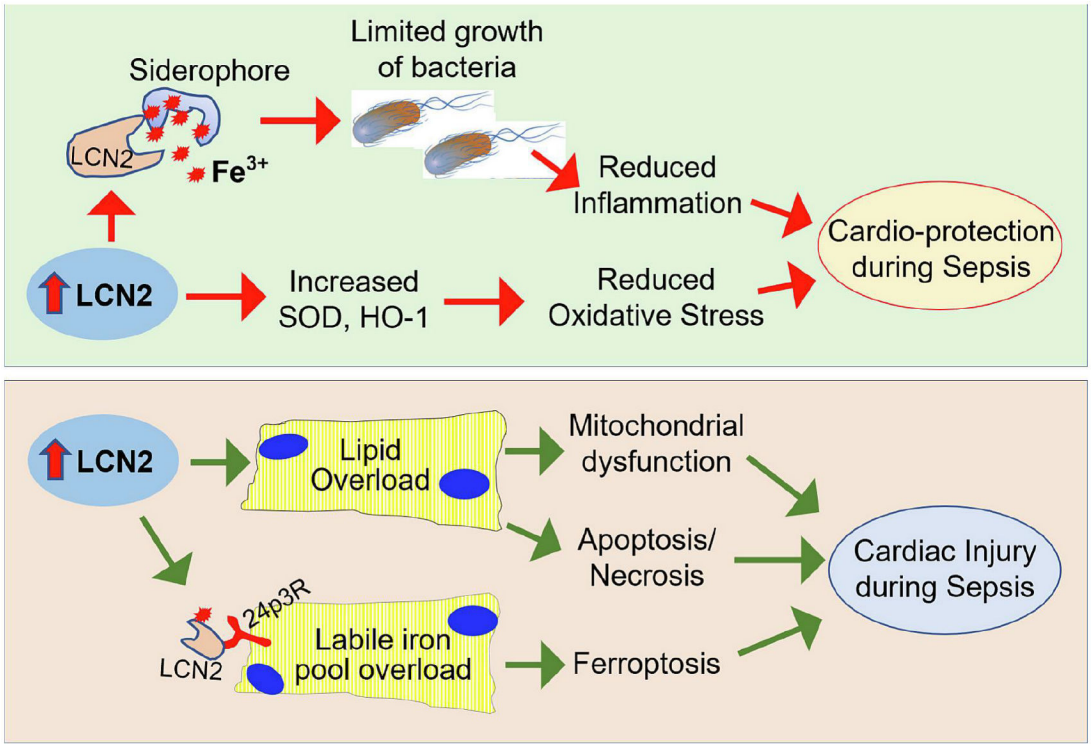

Figure 5: Paradoxical role of LCN2 in sepsis-induced myocardial depression.

Increased levels of LCN2 could bind siderophore and limit bacteria to use of iron for growth, leading to reduced inflammation. In addition, Lcn2 can upregulate the expression of superoxide dismutase (SOD) and heme oxygenase-1 (HO-1), leading to reduced oxidative stress. Therefore, LCN2-mediated anti-inflammation and anti-oxidation should provide protection against sepsis-induced cardiac dysfunction. However, LCN2 is able to promote lipid accumulation and labile iron pool overload in cardiomyocytes, leading to apoptosis, necrosis, and ferroptosis, which exaggerate sepsis-induced cardiac injury.

Table1.

List of the 24 LCN-like genes in the human and mouse—with gene symbols, chromosomal location, and their similarity, expressed as percent identity (%).

Gene symbol (human)	Chromosome	Gene symbol (mouse)	Chromosome	Similarity (identity%)
LCN1 (TLC, VEGP)	9q34	*NA*	NA	NA
LCN2 (NGAL)	9q34	*Lcn2*	2B; 2 22.09 cM	62
NA		*Lcn3–5*	2; 2A3	NA
LCN6 (UNQ643)	9q34.3	*Lcn6*	2; 2A3	74
LCN7 (TINAGL1)	1p35.2	*Lcn7*	4; 4D2.2	90
LCN8 (EP17)	9q34.3	*Lcn8*	2; 2A3	70
LCN9 (HEL 129)	9q34.3	*Lcn9*	2; 2A3	54
LCN10	9q34.3	*Lcn10*	2; 2A3	64
NA	NA	*Lcn11*	2; 2A3	NA
LCN12	9q34.3	*Lcn12*	2; 2A3	56
LCN13 (OBP2A)	9q34	*Lcn13*	2; 2A3	39
LCN14 (OBP2B)	9q34	*Lcn14*	2; 2A3	50
LCN15 (UNQ2541)	9q34.3	*Lcn15*	2; 2A3	39
AMBP (A1M)	9q32-q33	*Ambp*	3 B3; 433.96 cM	77
APOD (Apolipoprotein D)	3q29	*Apod*	16 B2; 16 21.41 cM	74
APOM (Apolipoprotein M)	6p21	*Apom*	17; 17 B1	81
C8G	9q34.3	*C8γ*	2 A3; 2 17.31 cM	76
ORM1 (AGP1)	9q32	*Orm1*	4 B3; 4 33.96 cM	49
ORM2 (AGP2)	9q32	*Orm2*	4 B3; 4 33.96 cM	44
PAEP (GD)	9q34	*NA*	NA	NA
PTGDS (L-PGDS)	9q34.2-q34.3	*Ptgds*	2 A3; 2 17.28 cM	72
RBP4 (Retinol-bing protein-4)	10q23.33	*Rbp4*	19 C2; 19 32.75 cM	86