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Review article

APLN/APJ pathway: The key regulator of macrophage functions

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ABSTRACT

Macrophages play key roles during cardiovascular diseases (CVD) and their related complications. Apelin (APLN) is a key molecule, whose roles during CVD have been documented previously. Therefore, it has been hypothesized that APLN may perform its roles via modulation of macrophages. Additionally, due to the widespread distribution of the CVD, more effective therapeutic strategies need to be developed to overcome the related complications. This review article collected recent information regarding the roles of APLN on the macrophages and discusses its potential chance to be a target for molecular/cellular therapy of APLN and the APLN treated macrophages for CVD.

1. Introduction

Apelin, which is known as APLN, is an endogenous ligand for the APLN receptor (APJ), an orphan G protein-coupled receptor [14]. APLN/APJ pathway plays key roles in several physiological responses of the mammalians including regulation of hypothalamic pituitary adrenal (HPA) axis, water balance, cardiovascular functions, and metabolic homeostasis [39]. Among them, the roles played by APLN/APJ pathway in the cardiovascular diseases (CVD) were strongly demonstrated (Folino, Montarolo, 2015). Interestingly, it has been reported that some gene polymorphisms within APLN/APJ genes might serve as predisposing factors in CAD [38]. Due to the complexity of the CVD, it has been hypothesized that APLN/APJ pathway mal-functions may be in association with several factors that are related to CVD. Accordingly, due to the positive effects of APLN/APJ pathway on the inotropic effect [51] and improvement of cardiac output [24], their effects on the risk factors of CVD are considered as future investigations.

Macrophages are a set of innate immune cells whose roles in the pathogenesis of CVD have been documented previously [13,59]. Accordingly, a sub-population of the cells, entitled macrophage foam cells, which are named Mox, show alternative functions and release their toxins and also free radicals on the endothelial cells, hence the vessel's plaques are produced which leads to cardiovascular related diseases such as atherosclerosis [1,4,7]. Several mechanisms play key roles in the production of the Mox phenotype of the macrophages including increased serum levels of low density lipoprotein (LDL) and glucose [56], however, investigators believe that several unknown factors may also participate in transforming the phonotype of the macrophages. Due to the approved roles played by APLN/APJ pathway in the CVD, it has been hypothesized that, APLN and its receptor may be considered as a candidate to alter or establish the macrophage functions.

Therefore, this review article was aimed to describe the effects of APLN/APJ pathway on the macrophage functions.

2. Introduction of APLN

APLN is an endogenous peptide, which has been isolated from the bovine stomach, using APJ as orphan G protein-coupled receptor [52]. Orphan receptors are a set of human cell receptors whose endogenous ligands are unknown [31]. Thus, APLN also has been described as using APJ to find its ligands. APJ, which is also known as APJR, HG11 and AGTRL1, was first discovered by O'Dowd, and its gene is located on 11q12.1 and has 1 exon [40]. Interestingly, APJ has 54% homology with angiotensin II receptor type-1 (AT1) (O'Dowd, Heiber, 1993). Although its ligand is APLN, it does not bind to angiotensin-II (Ang-II) (Lee, Cheng, 2000). The APLN consists of 77-amino acid as prepropeptide and is coded by a gene which is located on chromosome Xq25–26.1 (Lee, Cheng, 2000). After cleavage of signal peptide (22 amino acid of N-terminal), 55 preproapelin is produced and is cleaved from C-terminus and, so, produces several APLN isomers including

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Abbreviations

ACS	5′Acute coronary syndrome
AMPK	adenosine monophosphate-*activated protein kinase*
Ang II, Ang II	Angiotensin II
AT2R	receptor
APLN, APLN	Apelin
APJ, ATP	receptor
ABCA1	binding cassette transporter A1
ASP	Acylation stimulating protein
CVD	Cardiovascular diseases
M-CSF	Colony stimulating factor 1
cAMP	Cyclic adenosine monophosphate
DAG	Diacylglycerol
ERK1/2	Extracellular signal-regulated kinase 1 and 2
EH	essential hypertension
HPA	Hypothalamic pituitary adrenal
IP3	Inositol trisphosphate
LRG	Leucine-rich α2-glycoprotein
LPS	Lipopolysaccharide
LPL	Lipoprotein lipase
LDL	Low density lipoprotein
Mox	Macrophage foam cells
MIP	Macrophage inflammatory protein
miR	MicroRNA
MAP	Mitogen-activated protein
MCP1	Monocyte chemoattractant protein-1
NF-κB	Nuclear factor kappa light chain enhancer of activated B cells
NO	Nitric oxide
oxLDL	Oxidized low-density lipoprotein
PLCβ	Phospholipase C-β
PKC	Protein kinase C
PLC	phospholipase C
TLR4	Toll like receptor 4
TGF-β	Transforming growth factor-beta
ROS	Reactive oxygen species
VEGF	Vascular endothelial growth factor

APLN-36 (Sequence 42–77), 19 (Sequence 59–77), 17 (Sequence 61–77), 13 (Sequence 65–77), 12 (Sequence 66–77), 11 (Sequence 67–77) and 10 (Sequence 68–77), all forms of which are biologically active [18,35]. Kawamata et al., suggested that long and short forms of apelin may vary between different tissues [25]. Interestingly APLN isomers levels alter in different conditions in healthy and diseased individuals and in special situations such as pregnancy (Lv, Li, 2013).

Interaction between APLN and its receptor on the various cells may

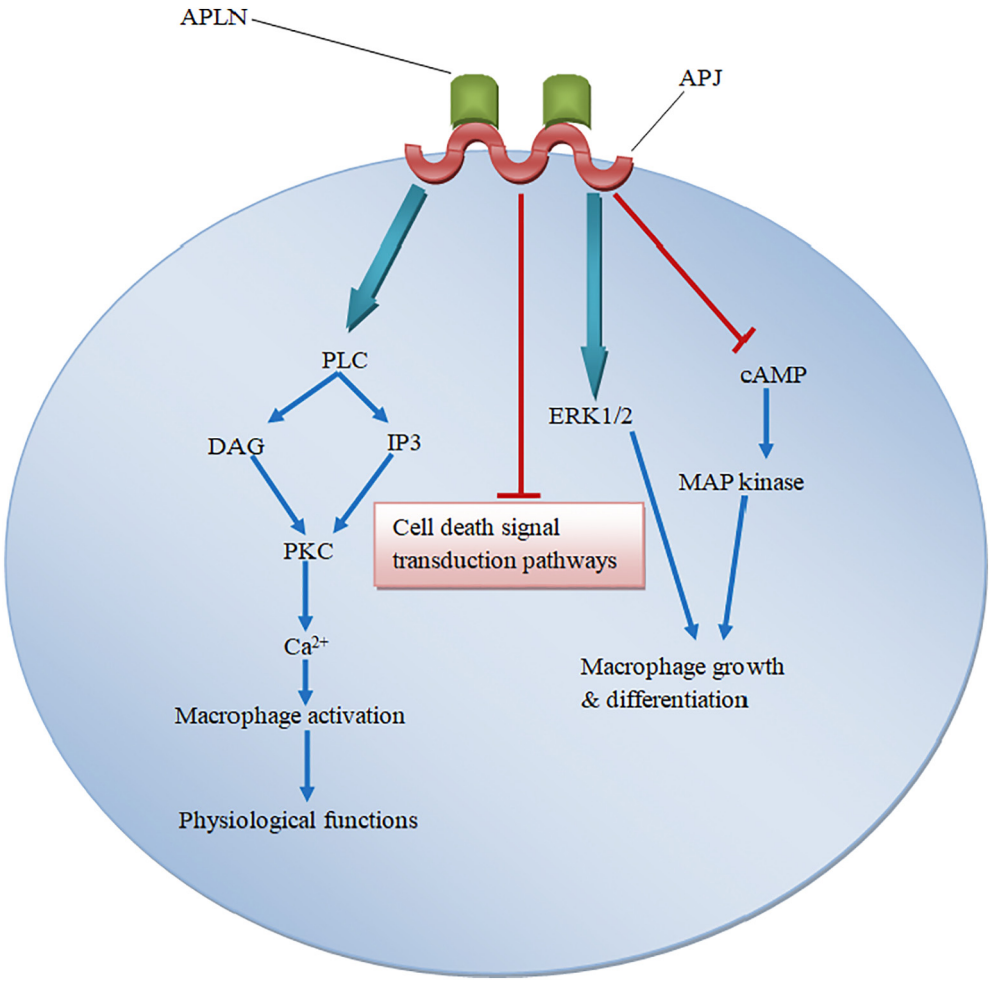

Fig. 1. The roles of APLN in the development and growth of macrophages. APLN induces ERK1/2 and MAP kinase pathways to activate the intracellular molecules and transcription factors involved in the activation of the genes, which participates in the growth and differentiation of macrophages. The APLN/APJ interaction also leads to activation of PLC and then production of DAG and IP3. The products are the activators of PKC and then elevation of cytoplasmic Ca^{2+} to activation of macrophages for physiological functions. APLN/APJ pathway also suppresses cell death signal transduction pathways and leads to survival of the cell.

be associated with different intracellular signaling. Interaction of APLN with its receptor may lead to activation of phospholipase C-β (PLCβ) and consequently increased intracellular Ca^{2+} in the target cells [68]. Increased Ca^{2+} can be a potential inducer of Ras, Raf, MEK and ERK pathways activation (Szokodi, Tavi, 2002). APLN/receptor interaction is also associated with the activation of JNK/IRS1/GSK pathway [63]. PI3K is another molecule, which is activated following APLN/receptor interaction. PI3K activation can lead to activation of its downstream molecule entitled AKT and then phosphorylation of mTOR and eNOS and finally production of the free radicals, including nitric oxide (NO) (Yu, Tang, 2014). The effects of APLN/receptor interaction on the activation of AMP kinase (AMPK) has also been reported by Than and colleagues [54]. AMPK not only directly induces activation of eNOS, it also indirectly influences activation of the molecule via up-regulation of AKT molecule (Than, Cheng, 2012). However, APLN is able to inhibit some pathways including transforming growth factor-beta (TGF-β) dependent signaling pathways and adenylyl cyclase enzyme [57].

3. Macrophages; the classification and functions

Macrophages are the main immune cells for clearance of the excess modified lipoproteins, which are accumulated in the neointima, the cells become engorged with lipids, so the macrophages no longer emigrate from the plaque [66]. This is a main reason for induction of complicated atherosclerotic lesion. It has been documented that macrophage differentiation is an irreversible process, however, it appears that macrophage polarization is reversible [46]. Accordingly, it has been reported that macrophages can polarize to several types including M1, the cell which induces Th1 immunological responses, M2a, the cell that participates in the tissue remodeling and endocytosis, M2b, which is a potential immunoregulatory cell, M2d, the pro-angiogenic and tumor promotion cell and Mox, which is a pro-atherogenic cell with weakly phagocytotic functions [36]. Therefore, it appears that the macrophages play various roles during the human disorders and it may be related to the microenvironment of the cells in the target tissues.

Due to the fact that atherosclerosis is a main cause of CVD, it has been demonstrated that the macrophages, especially Mox cells which are the main sources of heme oxygenase, alter their functions in the microenvironment of the inflamed vessels and heart tissue to damage the target cells and make atherosclerotic plaque [58].

4. APLN/APJ pathway and cardiovascular functions and diseases

It has been demonstrated that APLN/APJ pathway is one of the main mechanism to modulate the physiological functions of the cardiovascular system. Accordingly, it has been reported that APLN/APJ pathway plays key roles in the reduction of arterial blood pressure in a nitric oxide (NO)-dependent manner (Miranda, Heluy, 2018). Although it has been reported that APLN increases the production of NO in PI3K and AMPK dependent manner (see Fig. 1), it appears that it is down-regulated during cardiovascular diseases by APLN. It appears that up-regulation of NO in the physiological condition leads to increased expression of GLUT1 and GLUT3 to increase glucose uptake [55]. The APLN/APJ pathway also facilitates neovascularization through paracrine activities [53]. It has also been demonstrated that the APLN/APJ pathway significantly participates in the reduction of systemic venous tone and cardiac preload and also induction of diuresis and promotion of inotropic effects [2,5,11]. APLN also suppresses myocardial fibrosis by inhibition of TGF-β signaling [43]. Thus, it seems that APLN/APJ pathway plays critical roles in the physiological functions of the cardiovascular system.

Due to the above information, APLN/APJ pathway may be considered as a protection mechanism to inhibit cardiovascular disorders. Recent information also confirms the hypothesis and revealed that APLN/APJ pathway can protect the cardiovascular system. For example, Gupta et al., reported that apelin-13, the major apelin isoform in the blood circulatory system, was significantly decreased in the patients with essential hypertension (EH) and acute coronary syndrome (ACS) when compared to controls [17]. Additionally, Cirillo et al., demonstrated that apelin-13 protects the patients from ACS via up-regulation of prothrombotic tissue factor in the nuclear factor kappa light chain enhancer of activated B cells (NF-κB) dependent manner [9]. The protective roles played by APLN/APJ pathway against atherosclerosis have also been demonstrated by Kostopoulos and colleagues [27]. In parallel with the investigations, Hara et al., showed that APLN/APJ pathway plays key roles in the induction of neovascularization independent of other neovascularization molecules, such as vascular endothelial growth factor (VEGF) [20].

Due to the fact that macrophages play significant roles during cardiovascular disorders, it appears that there are important interactions between APLN/APJ pathways and the functions of the macrophages during physiological and pathological conditions of the cardiovascular system.

5. APLN plays key roles in macrophage growth and survival

It has been documented that macrophages have a long half-life, as the tissue resident cells. Several molecules participate in the induction of growth, survival and inhibition of apoptosis. APLN is also a key molecule that participates in the phenomenon. Accordingly, previous investigations revealed that colony stimulating factor 1 (M-CSF) is an important molecule for macrophages' growth and differentiation in Ras-dependent extracellular signal-regulated kinase 1 and 2 (ERK1/2) and mitogen-activated protein (MAP) kinase pathways dependent manner [47]. Consequently, apelin induces ERK1/2 pathway through coupling with APJ/Gi2 subunit [3] and activates MAP kinase pathway by suppression of adenylyl cyclase, and then reduces cyclic adenosine monophosphate (cAMP) in the macrophage, which is a main inhibitor of MAP kinase pathway [70]. Thus, APLN is an inducer of macrophage development. It has been documented that APLN protects macrophages from apoptosis. For example, Hartmann et al., reported that APJ is a key receptor for interaction with some biosynthesized molecules, such as 4-fluoro- N′-[1-(2-pyridinyl) ethylidene] benzohydrazide, to reduce the cytotoxicity of anthrax lethal toxin and modulates cell death signal transduction pathways [21]. APLN can also protect macrophages from hypoxia-induced apoptosis and enhances cell migration [60]. Moreover, APLN/APJ interaction is associated with activation of the cells by phosphorylation of phospholipase C (PLC) to produce diacylglycerol (DAG) and inositol trisphosphate (IP3). The products are essential for activation of protein kinase C (PKC) and elevation of the intracellular Ca^{2+} [28]. Given the evidence above, APLN is a main molecule that participates in the development of macrophages and its related physiological functions and cell survival. Fig. 1 describes the roles of APLN in the development and survival of macrophages.

6. The roles played by APLN in regulation of pathological roles of macrophages

Although APLN plays crucial roles in the induction of macrophage physiological functions, it has been hypothesized that APLN acts as a key regulator of macrophages functions during the pathological situations. Most investigations revealed that APLN modulates macrophage to ameliorate human/animal model pro-inflammatory based diseases. Accordingly, Charo et al., reported that apelin-13 significantly reduces the formation of macrophage foam cell through increasing ATP-binding cassette transporter A1 (ABCA1) protein levels. Apelin-13 increases expression of ABCA1 via activating the PKCα pathway and suppression of calpain activities (Charo, Ho, 2009). The results were also confirmed by Liu et al., who showed that apelin-13 increased ABCA1 expression via activation and suppression of PKCα and calpain pathways, respectively, and thereby enhanced the cholesterol efflux and decreased foam cell formation [33]. Zhang et al., revealed that apelin-13 by activation

of APJ/PKCα/miR-361-5p signaling pathway repressed the expression of lipoprotein lipase (LPL) in THP-1 macrophage-derived foam cells [67]. Previous investigations proved that macrophage-derived LPL is a key factor for development of atherosclerosis via accelerating lipid accumulation or production of pro-inflammatory molecules [26]. Apelin-13 also inhibits formation of foam cell through activation of Class III PI3K/Beclin-1-mediated autophagic pathway [61]. Foam cells play significant roles in the pathogenesis of atherosclerosis, so APLN may be considered as anti-atherosclerotic molecule by inhibition of foam cell formation. Latroche et al., demonstrated that APLN is a main molecule that participates in the myogenesis and angiogenesis by modulation of macrophage functions [30]. Further information regarding the positive roles played by APLN against macrophages-related atherosclerosis has been documented by Cui and colleagues [10]. They reported that APLN suppressed production of the oxidized low-density lipoprotein (oxLDL) in the macrophages (Cui, Ren, 2017). The investigators via down-regulation of APLN by using microRNA (miR)-497 demonstrated that the cells under treatment of miR-497 suffered from lipid accumulation in macrophages (Cui, Ren, 2017). Thus, APLN is a key modulator of macrophages in the pathological forms, especially in the foam cell format.

Moreover, APLN can regulate expression of the molecules involved in the inflammation and fibrosis. For instance, a study by Izgut-Uysal et al., demonstrated that APLN is an essential mediator for inhibition of the activated macrophages [23]. Interestingly, they reported that apelin-13 significantly decreased the mice peritoneal macrophage phagocytosis and chemotactic activities and the production of TNF-α and IL-6 by the cells (Izgut-Uysal, Gemici, 2017). To confirm the results, the investigation showed that using F13A, as APJ antagonist, prevented the suppressive effects of apelin-13 (Izgut-Uysal, Gemici, 2017). Previous investigations proved the significant roles played by TGF-β in the pathogenesis of tissue fibrosis [64]. Interestingly, the potential inhibitory effects of APLN on the fibrogenetic properties of TGF-β have been documented by Chen and colleagues [6]. Besides, the crucial relations between atherosclerosis and inflammation have been demonstrated previously [42]. Several molecules participate in the induction of inflammation during CVD, including the interaction of type 2 angiotensin II (Ang II) and its related receptor, Ang II receptor (AT2R) on peripheral macrophages [49]. APLN is a key molecule to inhibit AT2R action and, hence, decrease inflammation [50]. Moreover, it has been reported that using Losartan (the antagonist of Ang II) could lead to up-regulation of apelin, then attenuate macrophages migration [37]. In parallel with the study, Zhang and colleagues showed that administration of apelin-13 results in protection against lipopolysaccharide (LPS)/macrophages-induced acute lung injury in toll-like receptor 4 (TLR4) dependent manner, which is an inducer of pro-inflammatory cytokines production [65]. APLN reduces the pro-inflammatory injuries via inhibition of NF-κB activation and, consequently, decreased reactive oxygen species (ROS) formation in a macrophage cell line, Raw264.7 cells (Zhang, Chen, 2018). Yang et al., proved the results and demonstrated that APLN reduced the expression of Monocyte chemoattractant protein-1 (MCP1), MCP3, macrophage inflammatory protein (MIP)2, MIP1β and TNF-α in the Raw264.7 cells in NF-κB/JNK signal pathway dependent manner (Yang, Bai, 2015). An in vitro study on differentiated 3 T3-L1 adipocytes and RAW264.7 macrophages cells revealed that insulin down-regulated pro-inflammatory molecules in association with up-regulation of apelin [16]. The entire documents demonstrate the protective roles played by APLN during the macrophages based diseases. Another investigation on the effects of the APLN on the macrophages revealed that the molecule attenuates LPS-induced liver injury [69]. Interestingly, they reported co-administration of Fc-apelin fusion protein with LPS significantly attenuated LPS-related apoptosis, ROS production, hepatic macrophage infiltration, TNF-α and IL-6 gene expression and serum ALT elevation in the liver and in a macrophage cell line, Huh-7 cells (Zhou, Yang, 2018). APLN also down-regulates TNF-α, IL-1β and MIP-1 α/β in mice with cerulein-induced chronic pancreatitis by inhibition of NF-κB in the macrophages [19]. Another investigation demonstrated that macrophages are the main cells to

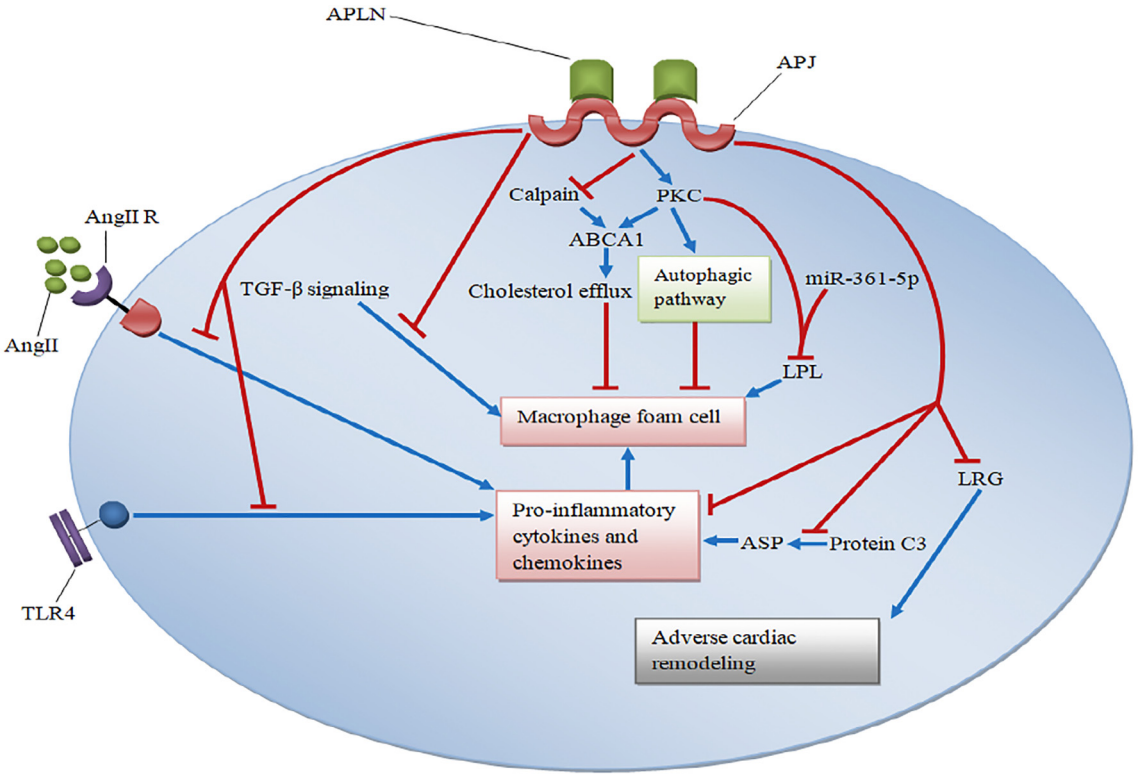

Fig. 2. The regulatory roles of APLN in macrophage functions. APLN suppresses foam cell formation by increasing in cholesterol efflux and autophagic pathway as well as inhibition of AngII R, TLRs and TGF-β signaling pathways, LPL, LRG and also conversion of protein C3 to ASP.

induce inflammation during obesity and diabetes by increased conversion of protein C3 to acylation stimulating protein (ASP) [34]. Interestingly, the study revealed that APLN/APJ pathway reduced protein C3 conversion to ASP by the macrophages (Lu, Gauvreau, 2013). Apelin also reduces UVB-induced number of CD11b-positive macrophages [48]. Furthermore, the anti-inflammatory effects of apelin on the macrophages lead to it being introduced as an inflammatory antagonist molecule to reduce myocardial impairment in sepsis shock [41]. The regulatory effects of apelin on the macrophages have also been demonstrated in another in vivo investigation that shows the inhibitory effects of the molecule on the LPS-induced vascular leak by macrophages [44]. Apelin also inhibits aortic aneurysm formation via suppression of macrophage-related inflammation, including production of the pro-inflammatory cytokines and chemokines [32]. Inhibition of APJ/APLN pathway leads to activation of Kupffer cells and TNF-α and IL-6 secretion and as a consequence enhances early phase liver regeneration after hepatectomy [62].

Due to the roles played by PALN in regulation of inflammation and fibrosis, Kumagai et al., showed that APLN/APJ pathway is a key factor for inhibition of adverse cardiac remodeling after MI, which is mediated by Leucine-rich α2-glycoprotein (LRG) molecule [29]. Some evidence showed that expression of apelin is increased in human atherosclerotic coronary artery and specially localized to the atherosclerotic plaque, the investigations proved that it is associated with decrease in receptor density [45]. However, it appears that up-regulation of apelin in this situation is a response to APLN/APJ signaling pathways, because lack of APLN/APJ signaling.

Collectively, it appears that APLN modulates macrophage activation via several pathways (Fig. 1). Although some investigations were performed on other human macrophage-related diseases, due to the fact that altered macrophages are the main parts of the cardiovascular disorders, hence it may be concluded that APLN may have an effect on the macrophages during CVD too. The regulatory roles of APLN on the macrophages are presented in the Fig. 2.

However, some limited studies reported that APLN/APJ pathway may not affect macrophage functions. For example, Hara et al., revealed that activated macrophages had similar profile of pro-inflammatory cytokines and migration in either apelin-deficient or wild type mice (Hara, Kasai, 2013). Another investigation on mice model demonstrated that treatment of the animals with apelin-13 for 3 weeks not only did not alter the atherosclerotic plaques size, but it also potentially enhanced the stable phenotype of the lesion [15]. This evidence suggested that macrophage functions are complex and several molecules may alter macrophage functions. Therefore, the effects of APLN on the macrophages may be considered in parallel with other significant agents such as cytokines and other pro-inflammatory molecules.

Due to the roles played by macrophages in the CVD, and based on the regulatory effects of APLN on the macrophages it may be hypothesized that APLN may be supposed as a key target for molecular therapy of the diseases. Additionally, due to the roles of the macrophages in the diseases it may also be hypothesized that cell therapy using auto-macrophages treated with APLN could be considered as cell immunotherapy to overcome the cardiovascular disorder pathogenesis.

It is worthy to note that, APJ is a co-receptor for HIV to introduce to the macrophages [8,12,22]. Thus, the roles of APLN in the HIV infected patients need more attention.

7. Conclusion

APLN, consists of several isomers, all forms of which are biologically active and may alter APLN isomers levels in different conditions in human healthy and diseases, in special situation. APLN affects several intracellular signals such as: PLC, Ca^{2+}, NF-κB, Ras, Raf, MEK, ERK, JNK/IRS1/GSK, PI3K, AKT, mTOR and eNOS, AMPK, TGF-β, and cAMP. Interaction between APLN and its receptor on the various cells may be associated with different intracellular signaling pathways. Recent information has suggested that, APLN/APJ pathway may be considered as a protection mechanism to inhibit cardiovascular disorders.

Macrophages have APJ, and APLN plays a central role in development, survival and function of macrophages. On the other hand, macrophages, as a principal component of immune system, play a central role in the inflammation, especially in the arthrosclerosis and CVD.

Overall, due to widespread effects of APLN, especially on the immune system, it is suggested that the effects of APLN on the macrophages be considered in parallel with other significant agents of inflammation, such as cytokines and other pro-inflammatory molecules in arthrosclerosis and CVD conditions.

Conflicts of interest

The authors declare no conflicts of interest.

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