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REVIEW ARTICLE

Molecular underpinning of association between PCSK9 and cardiovascular disorders and physical predictors of ischemic myocardial injury, cardiac arrest, and atrial fibrillation

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PCSK9 is involved in the cholesterol mechanism by lowering the number of low-density lipoprotein receptors in the plasma. This capacity of PCSK9 may infer its therapeutic benefits to treat hyperlipidemia and other lipid-associated conditions, mainly cardiac diseases. This review investigates the underlying mechanism through which PCSK9 is associated with cardiovascular diseases based on the available data. Several well-known molecular pathways confirm high PCSK9 levels when combined with acute myocardial infarction and atrial fibrillation. Moreover, this review highlights the risk of CVDs associated with physical predictors, such as age, diabetes, high BP, smoking, and PM-10. Mechanistically, PCSK9 has proven to be a promising drug for the treatment of infarcts and arrhythmias in several clinical and experimental studies.

Keywords: PCSK9, cardiovascular diseases, atrial fibrillation (AFib), myocardial infarction, ischemia

INTRODUCTION

Cardiac disorders are among the primary drivers of ailment and fatalities in both advanced and developing nations. Myocardial infarction, cardiac arrest, tachycardia, and cardiomyopathy are among common cardiovascular disorders (CVD) that kill millions of people each year. Cardiac disorders are triggered by a multitude of factors both variable and invariable. The presence of various risk variables increases the perils of cardiovascular conditions. Studies to unearth the molecular pathways that induce cardiac abnormalities have been conducted multiple times. PCSK9 (Proprotein convertase subtilisin/Kexin type 9) is an enzyme that degrades LDL receptors, ultimately reducing the cholesterol level in serum. PCSK9 suppressors have recently appeared as a potent cholesterol-lowering treatment. Nevertheless, accumulating statistics suggest that PCSK9 has a variety of impacts on cardiac disorders that are irrespective of LDL-cholesterol (LDL-c) modulation (Ding et al., 2018; Yang et al., 2020).

In mature cardiomyocytes, PCSK9 expression is constant (Schlüter et al., 2017). However, PCSK9 transcription is modulated mainly by the several elements located on the proximal promoter, such as sterol regulatory element (SRE), hepatocyte nuclear factor 1 (HNF1), and histone nuclear factor P. (HINFP). Cholesterol-lowering statin treatments trigger SRE-binding protein 2 (SREBP2) to move back to the nucleus and adjoin with the SRE motif, thus enhancing the PCSK9 expression in HepG2 cells (Dubuc et al., 2004). Also, anti-diabetic medications pioglitazone and Insulin stimulate PCSK9 transcription through SREBP2 (Shan et al., 2021) and SREBP1c (Morelli et al., 2019) respectively.

After an acute myocardial infarction (AMI) incidence, PCSK9 expression in the blood or on the surface of the heart may elevate dramatically. AMI-induced pathophysiology can significantly raise PCSK9 levels in hepatocytes (Ding et al., 2018).

Myocardial Infarction also increases the transcription of hypoxia-inducible factor (HIF)-1α in cardiac cells, which enhances PCSK9 expression. PCSK9 may initiate apoptosis in immature cardiomyocytes (Ding et al., 2018). The process involves the ROS-ATM-LKB1-AMPK pathway as shown in Fig. 1 (Zhou et al., 2014). Moreover, enhanced expression of PCSK9 in cardiomyocytes activates the NF-κB via canonical and non-canonical pathways to stimulate macrophages to secrete proinflammatory cytokine that ultimately endorses cardiac cell death. PCSK9 also enhances platelet activation in atrial fibrillation (AFib) individuals by reducing FVIII hepatic elimination, it may raise the incidence of thromboembolism (Goettsch et al., 2016).

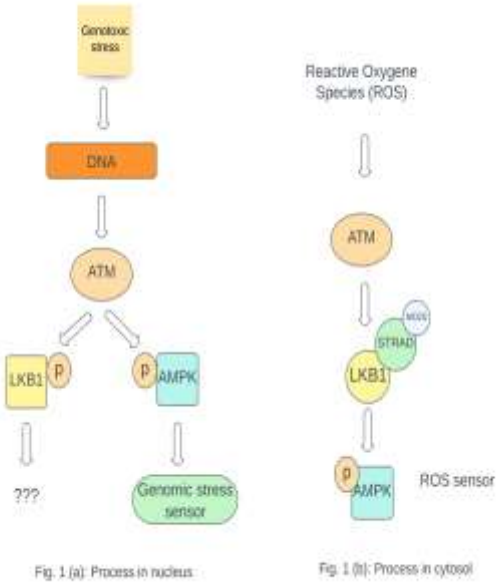

Figure 1: ROS-ATM-LKB1-AMPK Pathway in nucleus and cytosol

According to statistical research, plasma PCSK9 levels are inversely related to heart condition risk factors. Circulating PCSK9 levels, for instance, may arise with aging (Vlachopoulos et al., 2019). PCSK9 concentrations in the body are higher in postmenopausal females than in premenopausal females (Ooi et al., 2015), and systemic concentrations in females have a stronger positive relationship with systolic blood pressure as compared to that in males. PCSK9 may therefore be involved in the development of diabetes mellitus, a disorder that impairs insulin production (da Dalt et al., 2019). The conclusions from human and rodent investigations concentrating on PCSK9 in cardiac disorders are reviewed in detail in the following subsections, and probable linked molecular pathways are discussed.

2 PCSK9 and cardiovascular disorders

2.1 Association between PCSK9 and ischemic myocardial injury

A HUNT research in Norway found that blood PCSK9 values are in a positive correlation with AMI risk (Laugsand et al., 2016). Furthermore, accumulating experimentally induced data (Gao et al., 2018; Palee et al., 2019) shows that systemic or localized PCSK9 levels rise dramatically following ischemic myocardial damage. These analyses showed that PCSK9 values are strongly linked to the occurrence of ischemic myocardial infarction. The primary cause of elevated PCSK9 levels in the ischemic myocardial injury, on the other hand, is yet unknown.

Mechanistically, one prospect can be the way in which is that systemic inflammation promotes the upregulation of PCSK9. In a rodent model, expression of hepatic PCSK9 was the highest after 48 hours of AMI (Zhang et al., 2014). Also, it has been observed that the rat PCSK9 transcription was enhanced by systemic inflammation caused by lipopolysaccharides (LPS) (Wu et al., 2021). Additionally, the PEACE-Prospective AMI trial found a significant correlation between blood PCSK9 concentrations (taken during the acute stage) and high-sensitivity C-reactive total proteins (Gao et al., 2018). Another possibility can be the secretion of PCSK9 from cardiomyocytes after AMI, in addition to secreted PCSK9 by hepatocytes that can explain the rise in PCSK9.

PCSK9 is ubiquitously transcribed in mature mice cardiomyocytes, according to prior work (Schlüter et al., 2017). PCSK9 transcription in cardiomyocytes is dramatically increased in reaction to ischemia (Ding et al., 2018), and oxidized-LDL greatly boosts the level of PCSK9. PCSK9 mRNA level in cardiac cells is also increased by both Hypoxia/reoxygenation (H/R) (Yang et al., 2020) and ischemia/reperfusion (I/R) (Palee et al., 2019). Another study found high levels of PCSK9 mRNA in the area encompassing the infarct location. PCSK9 transcription in cardiac tissue is increased when they are exposed to ischemia, and this may be prevented by HIF-1 siRNA. It is freshly demonstrated that IL-1 treatment raised PCSK9 values in mice given a high-fat meal; nevertheless, this rise was greatly reduced in IL-1β− /− rats (Ding et al., 2020). These researchers also discovered that when hepatocytes were grown with peritoneal monocytes obtained from IL-1β− /− rat, PCSK9 values was much reduced as compared to those in wild-type rodent (Ding et al., 2020). This data imply that IL-1β is involved in the transcription of PCSK9. Also, an increase in upregulation of PCSK9, and interleukins in the infarcted myocardium was observed in the experimental group (Wang et al., 2020). Ultimately, data shows that IL-1β may contribute to PCSK9 overexpression.

As a result, higher PCSK9 levels may be caused by both systemic inflammation and heart damage.

According to a Mendelian randomization report, the PCSK9 SNP (rs11206510) exhibited the second smallest connection with higher LDL- cholesterol concentration but the third-largest influence on the probability of AMI among the top ten SNPs linked to plasma LDL-c concentrations (Voight et al., 2012). Such data imply that PCSK9's impact on AMI may extend beyond LDLR breakdown facilitated by PCSK9. Enhanced phagocytosis and high PCSK9 transcription were identified mostly in the zone surrounding the infarct location in a left coronary artery (LCA) ligation experiment (Ding et al., 2018). Further studies showed that modulation of the ROS-ATM-LKB1-AMPK pathway appears to be important in PCSK9-regulated apoptosis. According to these researchers, oxygen deprivation enhances PCSK9 transcription and ROS generation in a schedule-dependent way. PCSK9 transcription is also increased in cardiomyocytes when ROS inducers are used. On the other hand, mPCSK9 stimulates ROS production in a dosage-dependent way. As a result, they hypothesized that this pathway may be involved in PCSK9-induced phagocytosis in immature cardiomyocytes. Furthermore, a great deal of cardiomyocyte death was observed with H/R-prompted cardiac tissue damage (Yang et al., 2020).

Culturing Half Life-1 and macrophage RAW 264.7 cells together under Hypoxia/reoxygenation setting exposed that PCSK9 stimulates the inflammation reaction via deploying NF-κB signaling axis which activates macrophages to secrete proinflammatory interleukins. Besides, these cytokines ultimately reduce cardiomyocyte capacities and augment apoptosis in the co-culture arrangement. Chemokine (CC-motif) ligand 2 (CCL2) is a well-known promising target for NF-κB (Kircheis et al., 2020). The literature review has confirmed that CCL2 plasma values are distinctly augmented in individuals with AMI (Koper-Lenkiewicz et al., 2020) and CCL2 is exceedingly upregulated in mice-infarction experiments (Liu et al., 2018). Blocking the CCL2 expression using the deletion mutant of CCL2 reduced ventricular cavity dilation, contractility, and inflammatory cell infiltration in the left ventricle.

Exogenous treatment of several non-specific LRP1 blockers, for instance, 1-antitrypsin (Potere et al., 2019), has subsequently been shown to significantly attenuate infarct size on myocardium in the AMI and reperfusion clinical setup. Furthermore, giving the synthetic specific LRP1 blocker SP16 via intraperitoneal injection within half an hour after reperfusion resulted in fast Akt phosphorylation and a highly significant decrease in infarct size (Toldo et al., 2017). Considering the PCSK9 role in controlling LRP1, it may boost the immune response after MI, worsening infarct size, maladaptive cardiac restructuring, and cardiac arrest. According to the results, PCSK9 may be a therapeutically beneficial intervention to treat AMI. Several PCSK9 SNPs, such as rs11206510 are frequently related to a lower chance of young-onset acute myocardial infarction (Yu et al., 2017). In a left coronary artery-ligation experiment, pre-treatment with PCSK9 blockers decreased infarct sizes to 20%–30%, enhanced myocardial contractile function to 25%, and significantly decreased phagocytosis after LCA ligation.

Additionally, in an I/R model, a PCSK9 antagonist was observed to enhance left ventricular efficiency and mitochondrial biogenesis. Latest therapeutic trials have reliably shown that a PCSK9 blocker has no influence on pro-inflammatory cytokines (Trankle et al., 2019) and lowers the total frequency of myocardial infarction in individuals with pre-infarction or stable angina (White et al., 2019). These findings imply that PCSK9 antagonists have cardioprotective as well as atheroprotective roles

2.2. Association between PCSK9 and cardiac arrest

PCSK9 might play an imperative function in the progression of cardiac arrest/heart failure (HF). A 2017 BIOSTAT-CHF analysis suggested that plasma PCSK9 values are strongly linked with the probability of all-cause death in individuals with progressive HF (Bayes-Genis et al., 2017). Additionally, an animal study by Schlüter et al. confirmed decreased contractility of cardiomyocytes by initiating PCSK9 mRNA transcription, when treated with ox-LDL for 24 hours (Schlüter et al., 2017). Furthermore, another study revealed that systemic PCSK9 values are negatively associated with left ventricular ejection fraction (LVEF) in individuals with AMI (Jadczyk et al., 2019). Similarly, a study with only 25 participants conducted by Jadcyzyk et al. has shown a significant trend of association between plasma PCSK9 and LVEF changes ($P > 0.05$) (Bae et al., 2018). The study's variance was most possibly due to the short number of respondents. As a result, bigger sample size is necessary to assess the association of PCSK9 with HF. It is generally understood that N-terminal pro-brain natriuretic peptide (NT-proBNP), a valuable diagnostic biomarker of cardiac arrest, is markedly higher in these patients and is thought to be the outcome of myocardial remodeling.

Some latest pieces of literature discovered that NT-proBNP is significantly correlated with PCSK9 in individuals with both AMI (Bae et al., 2018) and cardiac arrest [28]. The mechanics behind their correlation are undisclosed. It is customarily documented that PCSK9 targets the LDL receptor, leading to higher LDL and ox-LDL plasma concentrations. Consequently, in this review, it is proposed that PCSK9 may increase BNP production in heart cells via boosting ox-LDL amounts. Furthermore, as a PCSK9 target protein, CD36 is predominantly abundant in vascular endothelium and heart cells, and it partly controls long-chain fatty acid intake by the heart. Because free fatty acids are the main power supply in the myocardium, CD36 insufficiency may be linked to cardiac injury-related cardiac failure and myocarditis (Dehn & Thorp, 2018).

Downregulation of CD36 restricts fatty acid delivery to the post-AMI myocardium and extended leukocyte activation, resulting in an expanded left ventricle (DeLeon-

Pennell et al., 2016). Furthermore, CD36 loss may hasten HF in individuals with already existing cardiovascular problems (Miyazaki et al., 2019). Since CD36 performs a critical part in HF pathogenesis, considerable research is required to understand the function of PCSK9-regulated CD36 breakdown in the etiology of cardiac arrest.

Studies revealed that LRP1, VLDLR, and HIF-1α are highly elevated in the myocardium of individuals with ischemia (Strickland et al., 2014). A scientific investigation discovered that LRP1 transcription is dramatically enhanced (>2 times) in the hearts of individuals with last-stage HF after cardiac surgery (Toldo et al., 2017). In addition, the LRP1 chain is found in the heart, and dissolved LRP1 amounts are greater in individuals with unexplained hypertrophic cardiomyopathies (Larson et al., 2022). The actual framework of elevated LRP1 expression in cardiac arrest is unidentified. Maladaptive remodeling is widely established to be related to a poor outcome in heart failure. One theory is that LRP1 reduces the negative remodeling of the left ventricle by regulating extracellular metalloproteinase. Oxygen deprivation was reported to enhance LRP1 production and MMP-9 activation in myocardial fibroblasts in a murine model of AMI (Revuelta-López et al., 2017). Hypoxic MMP-9 co-resides with LRP1 in ischemic myocardial fibroblasts in vivo and vice versa in an in vitro setting. These findings imply that LRP1 performs an important function in MMP-9 overexpression in myocardial fibroblasts following Infarction. LRP1 has also been linked to the modulation of MMP-2 and MMP-13 extracellular expression (Potere et al., 2019). Heart failure is also distinguished by reduced cardiovascular output and ventricular distensibility.

Recent research concluded that α2-macroglobulin may increase contractility via agonistic action on LRP1, and thwarts the harmful effects of accumulated LDL in cardiomyocytes. As a result, another suggestion is that LRP1 may show cardioprotective properties, leading to therapeutic applications in hypercholesterolemic heart diseases (Actis Dato et al., 2021). Overall, the data shows that in individuals with cardiac arrest, systemic PCSK9 values are considerably higher. The pathways behind elevated PCSK9 in heart failure are obscure. Considering the role of PCSK9 in the breakdown of LDLR, CD36, and LRP1, it is possible that PCSK9-modulated signaling is linked to the prognostication of cardiac arrest.

2.3 Association between PCSK9 and atrial fibrillation (AFib)

Since the discovery of the heart-gut axis hypothesis, mounting data has revealed that gut microbiota changes are linked to AFib (Yu et al., 2018). In individuals with acute inflammation, LPS, a byproduct of the intestinal microbiota, has been examined (Pastori et al., 2019). LPS-induced acute inflammation significantly enhances hepatocellular PCSK9 transcription in animals. Findings from the ATHERO-AFib cohort research continuously showed that plasma PCSK9 concentrations are substantially linked with LPS levels in individuals with AF ($P < 0.001$) (Pastori et al., 2019). These studies illustrate that AF may have a role in intestinal flora disruption and elevated gut-derived LPS concentrations, which can cause acute inflammation and hepatocellular PCSK9 overexpression. After controlling for statin usage and serum cholesterol, evidence from single-center retrospective research revealed that serum PCSK9 values, particularly high PCSK9 amounts (more than 1,600 pg/ml), are linked to an elevated risk of coronary incidents in patients with AF (Pastori et al., 2017). Plasma PCSK9 level and 11-dehydro-thromboxane B2 (11-dh-TxB2) are expressively associated, which implies that PCSK9 may endorse platelet activation in persons with AF (Cammisotto et al., 2020).

Fascinatingly, Cammisotto et al. found that blood PCSK9 values are positively linked with platelet activation markers and oxidative stress (Cammisotto et al., 2020). PCSK9 therapy also enhances platelet activation, oxidative stress, and phosphorylation of p38MAP kinase, p47phox, and phospholipase A2 in platelets. Platelets sensitized with antibodies against CD36 and PCSK9, as well as a p38 inhibitor, are unable to undergo these modifications. So, this review suggests that PCSK9 augmentation of platelet activation is linked to the NOX2-ROS-MAPK axis. Blood clotting factor VIII (FVIII) plays a vital role in blood clotting. Systemic FVIII joins to LRP1 and is then removed via hepatic LRP1. Moreover, Barbara et al. concluded in their research that LDLR is important in FVIII clearance (Lunghi et al., 2019)

PCSK9 may decrease liver FVIII elimination, augmenting the peril of arterial thromboembolism in AFib patients, due to its significance in modulating LRP1 and LDLR. Endothelial impairment is also seen in individuals with AF. Earlier research confirmed that apoE3/ApoER2 combination thereby increases endothelial NO generation, endothelium repair, and endothelial anti-inflammatory characteristics (Ulrich et al., 2014). Also, ApoER2 expression is observed in platelets, and ApoE might constrain platelet activation (Robertson et al., 2009). Consequently, PCSK9 probably plays a role in thrombus development in people with AF by degrading ApoER2.

Lastly, an accumulating body of evidence from pathological and experimental investigations shows that epicardial fat is linked to the prevalence, aggravation, and relapse of AF. PCSK9 production is boosted by a hormone released from adipose tissue. PCSK9 has also been linked to inflammation, vascular remodeling, and the production of reactive oxygen species (ROS). Resultantly, PCSK9 in epicardial fat could be linked to the development of AFib. Furthermore, hyperthyroidism is a well-established independent predictor for AFib. In non-obese participants, evidence from a comprehensive medical trial revealed that thyrotropin correlates favorably with PCSK9 ($P = 0.023$) (Kwakernaak et al., 2013). Plasma thyrotropin concentrations were shown to be substantially correlated with plasma PCSK9 concentrations in another similar investigation (Gong et al., 2017).

After treating HepG2 cells with recombinant human thyrotropin, the concentrations of PCSK9 mRNA and protein were shown to be simultaneously elevated. Overall, the link between PCSK8 and the development of AF has not been thoroughly established; further research is needed to validate PCSK9's role in AFib etiology.

3. Association between PCSK9 and physical risk factors

Cardiovascular disease is linked to age, obesity, diabetes mellitus (DM), high blood pressure (BP), environmental pollution, and smoking. PCSK9 levels in the blood have been linked to a variety of metabolic variables in past findings (Macchi et al., 2019). This review describes the relationships between PCSK9 and age, obesity, diabetes, high BP, and other variables including smoking and environmental pollution

3.1. Age

PCSK9 levels rise with age and are important at all developmental stages. PCSK9 expression was initially discovered in the hepatocytes on the 9th gestational day and in the epidermis, kidneys, digestive tract, and brain on the 15th gestational day in an in-situ hybridization histochemistry investigation (Seidah et al., 2003). PCSK9 appears to have a role in cerebral neuron specialization and embryonic kidney growth, according to further research. In youngsters who have had intracytoplasmic sperm injection, PCSK9 volume increases with age (Vlachopoulos et al., 2019). In teenage girls, blood PCSK9 values are likewise strongly associated with age (Melendez et al., 2019). Increasing amounts of data suggest that blood PCSK9 values are greater in postmenopausal females than in premenopausal females (Gosh et al., 2015). There are also more than 40 clinical publications available on PubMed addressing the link between systemic PCSK9 values and age in people. Among them, 45 percent of the publications found a positive correlation between systemic PCSK9 values and age, 47.5 percent did not find a substantial correlation, and only 7.5 percent found an inverse correlation. Customarily, the results indicate that PCSK9 might be in positive correlation with age and that this correlation can be controlled by various factors. Thus, PCSK9 reasonably mediates age-associated CVDs, although additional research is needed to confirm the premise.

3.2. Obesity

Several studies confirmed high PCSK9 levels in obese individuals as compared to the control group. Serum PCSK9 values are also significantly related to living fat aggregation in individuals suffering from nonalcoholic fatty liver disease (NAFLD) (Ruscica et al., 2016). Metabolic surgery is a reliable intervention for obese people to reduce serum PCSK9 and cholesterol levels (Boyer et al., 2017). Moreover, many hormones derived from fat tissues appeared to stimulate the PCSK9 transcription. For instance, resistin triggers PCSK9 expression, ultimately blocking LDL-receptor in HepG2 and liver cells (Melone et al., 2012). Another hormone leptin is positively associated with serum PCSK9 amount in healthy persons (Macchi et al., 2020).

Furthermore, leptin enhances HNF1α expression in HepG2 cells which leads to an increase in PCSK9 levels in plasma (Du et al., 2017). The functions of leptin and resistin in obesity-related CVDs suggest that PCSK9 may aid in the regulation of adipose tissue metabolism and heart disorders.

3.3. Diabetes mellitus

PCSK9 might be linked to the development of diabetes, which is categorized by insulin sensitivity. According to many demographic types of research, diabetes patients have considerably greater plasma PCSK9 amounts than healthy people (Ooi et al., 2015; Ibarretxe et al., 2016). Conversely, PCSK9 levels are linked to glucose tolerance measures. PCSK9 transcription is also considerably reduced in lab rats treated with streptozotocin (Momtazi et al., 2017) and mice with a hepato-specific insulin receptor deletion (Ibarretxe et al., 2016). As a result, elevated PCSK9 values may be linked to diabetes mellitus.

Globally PCSK9 knockout mice had reduced glucose elimination and insulin release, but not insulin resistance (da Dalt et al., 2019). However, PCSK9 loss results in bigger islet dimensions and higher cholesteryl esters, and insulin deposition in the pancreas. The buildup of cholesterol in beta cells promotes acute inflammatory response and a proclivity for beta-cell death. Extrahepatic localized PCSK9 loss elevates LDLR transcription in islets of Langerhans, culminating in enhanced cholesterol absorption via LDL-receptor in beta cells and their malfunction. Furthermore, a meta-analysis of 35 randomized clinical experiments including 45,539 subjects found that PCSK9 antagonist medication is not linked to the incidence of new diabetes or the aggravation of already existing diabetes (Karatasakis et al., 2017). The underlying mechanism PCSK9 blockers don't enhance the risk of diabetes is unknown. PCSK9 blockers may have a trivial effect on the LDL-receptor in beta cells, nonetheless, future research is needed to fully understand the reason.

3.4. High Blood Pressure (BP)

Past research dealing with PCSK9 and high BP has included study subjects based on different criteria. Therefore, the current relationship between them is contentious. However, the literature review suggests that there seems to be a strong relationship between PCSK9 and high BP in females as compared to males. Berger et al. found that PCSK9 impairment causes a small but considerable drop in BP in female mice (Berger et al., 2015) and vice versa in male mice.

PCSK9 controls BP through methods that are not completely grasped. Renal parenchymal high BP is the most prevalent and PCSK9 is activated in the kidneys

constantly. PCSK9 concentrations in the body were shown to be higher in individuals with glomerulonephritis in a new analysis. PCSK9, which is released by the kidney, may play a role in renal parenchymal hypertension. Epithelial Na+ channels (ENaCs), critically select sodium ions to get absorbed through epithelia, hence ENaCs are crucial for BP regulation. Available evidence demonstrated that PCSK9 blocks ENaCs transfer in human embryonic kidney 293T cells protocol (Sharotri et al., 2012). So, another prospect might be that PCSK9 can influence BP via ENaCs modulation.

5.5. Smoking and Environmental Pollution

Both active and passive smoking stimulates immune response and oxidative stress and promotes the PCSK9 expression. In a case-control study, it was established that the PCSK9 may elevate BP when combined with smoking (Yin et al., 2012). Also, contact with particulate matter-10 for a long time was testified to be correlated with elevated plasma PCSK9 levels. In vitro, this correlation regulated by interferon-γ was confirmed by a univariate study in HepG2 cells (Macchi et al., 2019). So, it can be inferred that particulate matter-10 enhances the interferon-γ, an inflammatory factor which in turn promotes the PCSK9 expression, hence increasing the risk of CVDs.

CONCLUSION

PCSK9 is a target protein that has been the focus of cardiovascular research. The PCSK9-LDLR pathway is a remarkable discovery for the treatment of dyslipidemia. Systemic PCSK9 levels and several physical predictors are in association combined with CVDs irrespective of hypercholesterolemia. Myocardial Infarction induces localized and systemic inflammation. Systemic inflammation induces PCSK9 transcription in hepatocytes via SREBP2 and HNF1α. Localized inflammation, oxidative stress, and oxygen deprivation induce extrahepatic PCSK9 expression in cardiac cells which can lead to cardiomyocyte dysfunction. Higher circulating PCSK9 level is associated with cardiovascular conditions especially aggravating the disease in patients with cardiac arrest. Furthermore, patients with AFib experience heart-related complications due to PCSK9-induced platelet activation and blood clotting. PCSK9 inhibitors can diminish infarcts and boost ventricular contractility, so future studies involving PCSK9 and related mechanisms can give insight into pathways related to cardiovascular disease progression. Well-designed experiments are needed to gather the data of patients with AMI, HF, and AFib to validate anti-PCSK9 treatments.

CONFLICT OF INTEREST

The authors declared that present study was performed in absence of any conflict of interest.

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AUTHOR CONTRIBUTIONS

FT and FK designed and performleed the experiments and also wrote the manuscript. SR, US, and MK performed animal treatments, flow cytometry experiments, tissue collection, SN perform data analysis. HS and NJ designed experiments and reviewed the manuscript. All authors read and approved the final version.

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