Review Article

Molecular basis of acute coronary syndrome

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Cardiovascular diseases (CVD) comprise of various heart and blood vessels-related diseases. Acute coronary syndrome (ACS) is one of them. Basic researchers and cardiologists have witnessed landmark developments related to ACS and despite rapid refinement in our understanding; scientists are seeking answers for more questions. Scientists have mapped wide ranging proteins and intricate protein networks which play central role in the pathogenesis in ACS. In this review, we have attempted to summarize underlying causes of ACS. Better understanding of the disease pathology will enable us to get a step closer to an effective clinical management.

Key words: Acute coronary syndrome, signaling, therapy

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INTRODUCTION

Cardiovascular diseases (CVD) comprise of various heart and blood vessels-related diseases. Acute coronary syndrome (ACS) is one of them. Coronary artery disease (CAD), coronary heart disease (CHD), and ACS are the terms which most researchers still use interchangeably. However, the molecular biology of all these diseases is quite different. ACS is said to be a subclass of the CAD, and in the same context, CHD occurs because of the CAD. CAD may be asymptomatic; however, ACS always occurs with visible symptoms.[1] CAD occurs with the blockage of the coronary arteries with atherosclerotic plaque accumulation. As a result, the blood and oxygen flow towards heart decreases. When this condition worsens up, then it can cause unstable angina (UA) along with the myocardial infarction. It includes the ST-elevation myocardial infarction (STEMI) which the health professionals also refer to as Q-wave myocardial infarction. The other condition which can co-occur with the UA is the non-STEMI also known as non-Q-wave myocardial infarction. These conditions cause a massive blockage of blood and oxygen flow toward the heart which makes it a lethal disease among native Americans.[2]

Nausea, chest pain, dyspnea, muscular pain, lightheadedness, referred pain, vomiting, and diaphoresis are some of the symptoms present in patients suffering from ACS. Not all these symptoms necessarily present in the patient with ACS. Almost 4%–14% of these patients have the severe pain and the pain may be present in one arm both arms. The jaw, neck, shoulders, and backbone may also feel the pain and sometime the pain in this situation feel like radiating or travelling from chest to the arm and to the other arm.[3,4] Inflammation and has quite decisive role in the occurrence of the heart disease especially heart failure. Numerous inflammatory mediators have central roles in the development of heart-related inflammatory diseases. Whenever the accumulation of cholesterol in the vessel walls surpasses the levels kept under control by macrophages, cholesterol precipitates into cholesterol crystals. However, extensive research is required to study the exact cause and link between inflammation and these heart diseases such as ACS.[5]

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Low levels of 25 (OH) D have been reported to be associated with prevalent CADs[6].

An important study emphasized on the necessity of giving more attention to psychological factors in primary prevention levels with reference to the public welfare and quality of life of patients with CHD.[7] More importantly, acute stress, depression, hostility, and vital exhaustion have been interconnected with rise in the levels of pro-inflammatory cytokines. Therefore, psychological interventions are advantageous mainly in context of ACS patients.[8]

There are some good reviews related to underlying mechanisms of ACS.[9-15] In this review, we have summarized most intriguing seminal research works which refined our understanding about the pathogenesis of ACS.

INVOLVEMENT OF NLRP3

NLRP3 inflammasome is one of the most widely known NLR complex which are known to have role in CVD because of their critical involvement in innate immunity.[16,17] NLRP3 encodes for three domains which are NOD, LRR, and the Pyrin domain containing protein 3. The LRR domain further encodes the leucine rich repeat domain and forms the carboxyl terminal of the NLRP3 domain.[18] Countless researchers have described the crucial role of NLRP3 in various autoinflammatory diseases and its relationship with the IL-1 in case of inflammatory diseases.[19,20] Signals like stimulation of the cytokines and the activation of TLRs can induce and stimulate the NLRP3. The NLRP3 gene consists of the pyrin domains which constitutes the amino terminal of its expressed protein, a binding domain for the nucleotide in the central region and the LRR domain at the C-terminal of its expressed protein.[21] The LRR domain in NLRP3 aids in detecting any unusual and dangerous signals and then the whole gene acts accordingly.

Atherosclerosis is an inflammatory disease contributing towards ACS. It occurs due to the inequity between the mediators and inhibitors of the inflammatory system. This instability between the stimulatory mediators and the inhibitors results in the atherosclerotic plaque build-up in the arterial walls. Interleukin (IL-27) is a known cytokine with immunomodulatory properties in case of inflammatory diseases. The over expression of IL-27 can cause an increase in the atherosclerotic plaque buildup which leads to atherosclerosis. Moreover, patients with ACS and myocardial infarction have elevated levels of the IL-27 in their bloodstream.[22] NLRP3 inflammasome along with some other immune cells has proven key roles in stimulating the atherosclerosis inflammation. Any person having the atherosclerosis inflammation has cholesterol crystals and these crystals play a vital role in the activation of NLRP3 inflammasome and it furthers results in the activation of the IL-18 and IL-1 β which causes atherosclerosis [Figure 1].[23] Phagocytosis of cholesterol crystals causes lysosomal damage which is sensed by NLRP3 inflammasomes, resulting in the release of IL-1 β.[23] Expression levels of IL-1 β have been reported to be upregulated in atherosclerotic pathologies and connected to severity of the disease. In accordance with this approach, to target the downstream effectors of NLRP3 inflammasome, different pharmacological agents have been shown to be effective. Canakinumab, a monoclonal antibody (mAb) against IL-1 β significantly reduced risk of recurrent cardiovascular processes thus highlighting a critical role of IL-1 β in atherosclerotic pathologies. Incubation of the carotid plaques with cholesterol crystals led to higher amounts of IL-1 β. More interestingly, complement-activated product (C5a), displayed effective biological activities that resulted in inflammatory sequelae. Priming with C5a before incubation with cholesterol crystals considerably increased the release of IL-1 β and IL-18. Similarly, priming with the combinatorial treatment (C5a and tumor node factor) before stimulation with cholesterol crystals activated inflammation through induction of NLRP3-transcriptional networks in the plaques.[23]

Inflammasome complex comprises of various inflammatory proteins which have a crucial part in innate immunity against infections and pathogen invading. However, abnormal upregulation of these inflammatory proteins can cause serious inflammatory and autoimmune disorders. These diseases include numerous heart-related diseases and blood clotting disorders such as thrombosis. NLRP3 inflammasome is the only inflammasome which creates a strong relationship between inflammation and thrombosis.

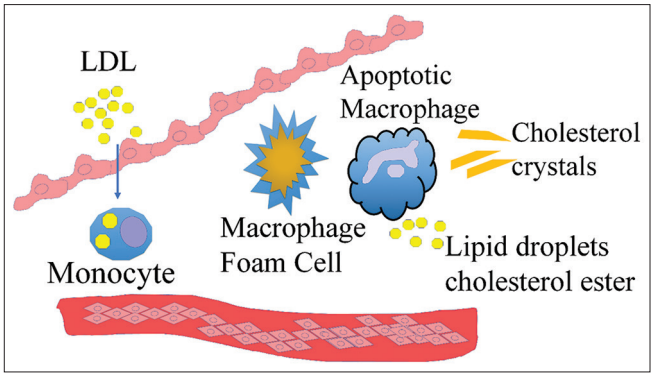

Figure 1: Plasma low-density lipoproteins (LDL) enter through the arterial wall. LDLs accumulate in mononuclear phagocytes through scavenger receptors. Later, lipid-laden macrophage foam cells die. Death of lipid-rich macrophage foam cells resulted in the accumulation of extracellular cholesteryl ester and cholesterol monohydrate crystals in the lipid-enriched necrotic cores of the plaque. Cholesterol crystals can trigger the activation of the inflammasome that generates biologically active version of the proinflammatory cytokines Interleukin-1 β (IL-1) and IL-18

The activation of the NLRP3 inflammasome gives rise to the maturation of the IL-18 and IL-1 β cytokines which fight against invading pathogens as part of innate immunity, but their upregulated expression gives rise to the inflammasome mediators which have a key role in thrombosis and atherosclerosis leading to ACS.[24,25]

These ILs have proven roles in aiding the inflammatory cascade and plague progression.[26] An important study conducted on patients having ACS provided interesting findings. As NLRP3 has a proven role in the atherosclerosis which leads to ACS so in this research rosuvastatin drug was given to the patients in optimized doses. This drug downregulated the expression of the NLRP3 and its other mediators thus relieving in atherosclerosis inflammation. At a concentration of 20 mg, Rosuvastatin significantly decreased the levels of NLRP3, cathepsin-B, and their downstream cytokines.[27]

Many researchers have proved that colchicine can also target the NLRP3 receptors and downregulate its expression and inflammation because of its anti-inflammatory properties especially in case of ACS.[28] ACS patients demonstrated significantly higher levels of CCL2 and CX3CL1. Colchicine use in ACS and CAD patients has been supported by findings from the LoDoCo trial and COLPLAST-ACS study.[19] As IL-18 and IL-1 β are the known cytokine inflammatory mediators induced by NLRP3, so researchers have used colchicine in order to block the NLRP3 inflammation cascade to prevent ACS and various other inflammatory diseases.[29,30] Statin drug is known to have therapeutic effects in case of hyperlipidemia and numerous hear-related diseases. Its anti-inflammatory and immunomodulatory properties have made it useful to use it against CVD. Several studies have shown its properties to target the NLRP3 inflammasome and various other downstream inflammatory mediators. The use of statin in patient with inflammatory diseases such as atherosclerosis can provide a relief by targeting the inflammatory mediators like NLRP3 which give rise to atherosclerosis.[31]

ACS comes with several complications and coronary microembolization (CME) is one of them which cause the myocardial infarction. When the NLRP3 inflammasome gets activated in ACS after the CME, then it stimulates the TLR4/MyD88/NF-κB signaling pathway which has central role in the myocardial inflammation after other inflammatory mediators. This signaling pathway has stimulating role toward the NLRP3 inflammation and ultimately gives rise to the inflammatory cascade in ACS. In order to inhibit the inflammatory mediators and NLRP3 inflammasome, inhibition of TLR4/MyD88/NF-κB is required. Inhibition of the TLR4/MyD88/NF-κB signaling pathway results in the reduction of the NLRP3 inflammasome and its mediators' release and helps to improve the cardiac condition in case of CME and ACS.[32] Several studies and case studies have been conducted to evaluate the nature of relationship between NLRP3 and ACS. In a recent study, case study was conducted including the normal individuals, patients with stable angina pectoris (SAP) and patients having ACS. In all these individuals the level of the platelet NLRP3 was evaluated using various molecular techniques. Individuals with ACS clearly represented higher levels of NLRP3 than those of the SAP patients and normal individuals which leads to the clear deduction that platelet NLRP3 co-occurs with the ACS.[33] A similar study was done to evaluate the correlation between severity of coronary atherosclerosis in patients with ACS with the level of NLRP3 inflammasome. When the follow-up of the individuals was taken for major adverse cardiac events, it clearly represented elevated levels of NLRP3 inflammasome in ACS patients. The results depicted that the levels of NLRP3 inflammasome increased with the severity of the coronary atherosclerosis.[34] Ticagrelor is known to have promising antiplatelet properties but recently its inhibiting properties for NLRP3 inflammasome has been discovered in patients with ACS. It has the ability to suppress the overexpressing NLRP3 inflammasome in macrophages which leads toward several dangerous inflammatory diseases including ACS independent of its novel role in $P2Y_{12}$ signaling pathway. Ticagrelor has also been approved by FDA as a therapeutic agent in the treatment of CAD.[35]

INVOLVEMENT OF DIFFERENT SIGNALING PATHWAYS IN ACUTE CORONARY SYNDROME

Reduction in the levels of miR-224 or hyperactivation of Transforming growth factor/Small body size Mothers Against Decapentaplegic (TGFβ/SMAD) cascade increased the intima surface and area of atherosclerotic plaques in thoracic aorta in rat with myocardial infarction.[36]

1% cholesterol diet increased miR-155 expression while conjugated linoleic acid blend supplementation led to downregulation of miR-155 expression in the aorta during atherosclerosis regression *in vivo*. miR-155 mimics effectively reduced anti-inflammatory proteins, BCL6, and p-STAT-3 in macrophages.[37]

miR-19b inhibited unstable plaque formation by the negative regulation of endothelial cell proliferation, migration, and angiogenesis. miR-19b exerted inhibitory effects on vulnerable plaque formation by inhibition of STAT3 signaling.[38]

IL-9 expression was higher in aortic arches in $ApoE^{-/-}$ mice fed with western diets.[39] Aortic plaque burden was noted to be reduced significantly in mice treated with IL-9 mAbs.

Moreover, the size of the plaques in the aortic roots was reduced in experimental rodent models after treatment with IL-9 mAbs. Furthermore, IL-9 mAbs considerably reduced the infiltration areas of macrophage and $CD3^+$ T cells in plaques. Interestingly, IL-9 induced VCAM-1 expression in murine aortic endothelial cells through STAT3-mediated cascade. VCAM-1 neutralization prevented IL-9-mediated increase in the size of plaques.[39]

Importantly, there was a significantly greater subpopulation of IL-17^+ FOXP3^+ T cells noted in the patients of ACS. Importantly, IL-17^+ FOXP3^+ cells are "inflammatory" Treg cells reported in the pathological microenvironment which fueled inflammatory activities in patients of ACS. Study provided proof of significant binding of STAT5 to the FOXP3 locus in STAT3-silenced cells. STAT5 overexpression led to an increase in the number of Treg cells but a decreased number of Th17 cells in ACS patients. STAT3 inhibition substantially suppressed the proportions of IL-17-producing cells but upregulated the expression of FOXP3 and enhanced the functions of Treg cells.[40]

INVOLVEMENT OF NONCODING RNAS

Noncoding RNAs have been widely associated with the regulation of gene expression in various contexts, including virtually all the aspects of development and pathogenesis.[41-48] In this section, we contextualize and discuss the emerging principles that define how noncoding RNAs play contributory role in ACS.

Circulating miR-221/222 levels in ACS patients have been reported to be elevated and positively correlated with the severity of the coronary artery lesions.[49]

Increase in the plasma levels of miR-146a-5p and miR-21-5p can be considered as circulating biomarkers for ACS patients.[50] Serum exosomal miR-146a has also been reported to hold potential as a novel diagnostic biomarker for ACS patients.[51]

miR-3646 knockdown has been shown to alleviate ACS by reversal of inflammatory responses.[52]

T-lymphocytes played critical roles in the progression of atherosclerosis, and inflammatory cytokines secreted by $CD4^+$ T-cells directly stabilized atherosclerotic plaques through activation of macrophages, thus leading to ACS. miR-let-7i overexpression suppressed apoptotic death in $CD4^+$ T-cells and improved the survival rate of the cells, whereas inhibition of miR-let-7i led to an increase in cell apoptosis. It was found that miR-let-7i directly targeted FasL and Fas in $CD4^+$ T-cells.[53]

miR-378c protected against atherosclerosis by direct inhibition of Sterile Alpha motif domain containing-1 (SAMD1).[54] miR-378c downregulation results in an increase in the VSMCs phenotypic modulation, which is a critical step in atherosclerosis. Importantly, phenotypic transition of VSMCs from the differentiated to de-differentiated state is accompanied by cellular proliferation and migration, which are the hallmark features of atherosclerosis. SAMD1 is a newly reported low-density lipoprotein (LDL)-binding protein. Binding of LDLs with SAMD1 on the cell surface promoted LDL oxidation and subsequent formation of the foam cells.[54]

Blood lipid levels and inflammatory contents were found to be reduced in ACS model of the rodents treated with miR-335-5p agomirs.[55] miR-335-5p overexpression effectively reduced lesion areas, consequently leading to a marked reduction in atherosclerosis in ACS mice. In addition, miR-335-5p upregulation reduced the lipid accumulation, hence causing a suppression of formation of the plaques.[55]

Based on the data provided by the World Health Organization, ACS is the leading cause of fatalities world widely. Because of the unexpected onset and speedy development, it is much needed to stop this disease at its early stages. Previously, various biomarkers used for the diagnosis of ACS include glycosylated hemoglobin (HbA1c)[56]), Cardiac troponin T (cTnT), Cardiac troponin I (cTnI),[57] phospholipid protein,[58] myoglobin, cTnI/cTnT (particularly the hypersensitive troponin I/T), B-type natriuretic peptide,[59] creatine kinase-MB, and gremlin 1, and macrophage migration inhibitory factor.[60] However, the limitation of these markers is that some of these also have elevated levels in other diseases than ACS. Human genome has more than 90% part specified to the noncoding RNAs (ncRNAs). This noncoding RNAs as the name shows they don't code for any protein, so they are considered as part of the genetic junk. Because of the abundant availability and their specialized effects upon the gene regulation at the posttranscriptional level and also because of their crucial role in the development of different diseases, they can be used as promising diagnostic markers for early detection of numerous diseases, especially CVDs.[61] These ncRNAs include micro RNAs (miRNA or miR), circular RNAs, and long noncoding RNAs. All these ncRNAs have a vital role in regulating the expression of genes as well as in the development of cardiac diseases.[62] Various studies have also reported the significant role of these ncRNAs in the early diagnosis of various CVD.[63]

In an important study, the role of circulatory miR-92a in patients having type 2 diabetes mellitus (T2DM) along with the ACS in CHD was evaluated. Two groups of individuals were included in this study. One is the DACS (patients having ACS along with the history of

T2DM), CACS (patients having only ACS in CHD). All these patients were examined for their serum level miR-92a in relation with blood lipid level, blood glucose level, and blood pressure. Patients of the DACS category represent higher levels of serum miR-92a in them which clearly makes it a promising diagnostic marker for detecting ACS in patients having T2DM.[64]

In a similar study, the serum level of miR-941 was checked in patients with stable angina (SA) and STEMI. When the examined serum results were compared then those patients who were suffering from STEMI had higher level of circulating miR-941 in their serum than those of the patient who has SA. Hence, the higher levels of the miR-941 in patients with STEMI confirmed that it can be used as an efficient diagnostic biomarker for CVD.[65]

In another case study, relation of the serum miRNA-499 and miRNA-210 was investigated against CVD. Patients with UA, non-STEMI (NSTEMI) (who had symptoms of chest pain which suggests that they may be suffering from ACS), and those having noncardiac chest pain (NCCP) were included. When their serum examination was done, then the patients who had NSTEMI and UA had elevated levels of both the miRNA-499 and miRNA-210 in comparison with those of the NCCP patients which makes both these miRNAs as effective biomarkers in the early diagnosis of ACS and other CHD.[66]

NATURAL PRODUCTS AS EFFECTIVE THERAPEUTIC AGENTS

Every year more than 5 million people have to go for the percutaneous coronary intervention (PCI) for the treatment of ACS.[67] Patients who are having the PCI also needs dual antiplatelet therapy (DAPT) along with the Clopidogrel (to block the receptors of P2Y12 signaling pathway) for the treatment of recurring events of chest pain and ischemic heart pains. However, the limitation of using only clopidogrel is that its antiplatelet response varies from individual to individual and can even increase the risk of ischemic events is patients with ACS. Moreover, patients having high platelet reactivity (HPR) can even suffer from stent thrombosis (ST) because of using clopidogrel as a single treatment.[68]

Natural products have re-gained the attention of researchers globally because of high-quality bioactive constituents and significant pharmacological properties.[69-75] Importantly, the identification of natural products having scientifically validated medicinal properties has skyrocketed. In the past few decades, pharmaceutical industry research into natural products has expanded at a breakneck pace.[76-79] Emerging evidence has started to illuminate the ability of natural products to ameliorate ACS in animal models.

Salvianolate potentiated the anti-platelet effects of clopidogrel plus aspirin in ACS patients.[80] Salvianolic acid B inhibited aggregation of the platelets and GPIIb/IIIa activation induced by ADP. Moreover, VASP is an important substrate of PKA (cAMP-dependent protein kinase), which phosphorylates serine-157 of the 3 phosphorylation sites on VASP. Salvianolic acid B enhanced phosphorylation of VASP in ADP-stimulated platelets. Salvianolic acid B blocked the interactions between ADP and P2Y12 receptor.[80] Clinical trials have provided evidence about significant effects of anti-platelet drugs including clopidogrel, aspirin as well as GP IIb/IIIa inhibitors in ACS patients. ACS patients can reap benefits from combinatorial treatments consisting of salvianolate and standard anti-platelet therapies, which require further in-depth research.

Suxiao Jiuxin pills not only reduced adverse cardiovascular events but also improved heart function and quality of life of ACS patients.[81]

For the treatment of these disorders, Chinese medicine specialists have been using Tongxinluo capsules (TCs) with notable efficacy against these diseases.[82,83] There are several pathways in human body which activates the platelets so to inhibit these platelets a single platelet therapy is ineffective.[84] Researchers used the antiplatelet therapy for the treatment of HPR in patients suffering from ACS. In addition to clopidogrel with DAPT they also used TCs, and the results displayed notable reduction in the HPR in ACS patients as compared to those who were treated with single clopidogrel.

Researchers investigated the use of Shexiang baoxin pills in individuals who were suffering from ACS with clopidogrel resistance. Patients having ACS along with the clopidogrel resistance were divided into two groups; one who was given the Shexiang baoxin pills along with that of the clopidogrel while the other group was treated with clopidogrel only. The platelet aggregation rate of the patients in the first group was quite less than that of the other one. Apart from that Shexiang baoxin pills in combination with the clopidogrel also enhanced the heart rate variability in patients with ACS.[85]

Maixuekang Capsule also has proven efficacy in reducing the platelet aggregation among ACS patients with ADP-induced platelet aggregation disorder.[86]

Future directions must emphasize on a better identification of traditional pharmacopeias to screen most potent and effective products which can ameliorate ACS.

CONCLUDING REMARKS

In this review, we have made efforts to provide a comprehensive landscape of the regulators which play instrumental role in the pathogenesis of ACS. Despite encouraging advancements in the biology and identification of clinically effective pharmacological targets, we still have to translate these findings more meaningfully in preclinical models.

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Conflicts of interest

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