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A survey on coronary heart disease related signal pathways, drug targets and pharmacological interventions

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Abstract

Coronary heart disease (CHD), the most common form of cardiovascular disease, is a chronic, multifactorial disease. With significant advances in our understanding of the pathophysiological process of CHD in recent years, more and more drug targets have been identified and adopted in drug discovery for CHD. In this review, a comprehensive perspective of pathological and pharmacological development of CHD was introduced through searching in multiple bibliographic sources. CHD related signal pathways (including 409 proteins), drug targets (including 101 proteins) and pharmacological interventions were summarized and visualized. The knowledge of these signal pathways and drug targets may facilitate new drug discovery and medicine intervention for CHD in the future.

1. Introduction

Cardiovascular disease (CVD) is the most common cause of death worldwide. It was estimated that around 23.6 million people will die from CVDs by 2030 and approximately half of these occurrences are directly related to coronary heart disease (CHD)[1,2]. CHD is the consequence of atherosclerosis with accumulation of atheromatous plaques within walls of coronary arteries that supply myocardium with oxygen and nutrients. The progress of CHD is characterized by its chronicity. It is particularly insidious in initial stages. Several risk factors such as cigarette smoking, hypercholesterolemia, hypertension, hyperglycemia and work stress have been demonstrated to be closely related to the processing of CHD. Acute myocardial infarction, arrhythmia, angina pectoris and heart failure are major clinical manifestation of CHD.

In the formation of atherosclerosis and CHD, endothelial cells (ECs), vascular smooth muscle cells (VSMCs), macrophages, T leukomonocytes, monocytes, mast cells, dendritic cells, platelets and cadiocytes interact with each other to damage normal functions of coronary artery and heart muscle [3-10]. Multiple intracellular and extracellular signal pathways containing hundreds of proteins participate in these interactions. A total of 413 CHD associated proteins were listed in Supplementary Table 2. Some of these proteins, such as 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase), angiotensin-convertion enzyme (ACE), and angiotensin (Ang Ⅱ) receptor, have been identified as drug targets. Drugs designed according to these targets have been playing important roles in the treatment of CHD.

In this review, we summarized CHD related signal pathways, drug targets and pharmacological interventions (including combination therapy) in clinic through searching in multiple bibliographic sources. By doing so, a comprehensive knowledge of ligands and targets relevant to CHD can be shown and further facilitate the drug discovery.

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2. Cells, pathways and proteins related to CHD

CHD is a chronic disease in which blood flow is obstructed through coronary arteries that supply heart with oxygen-rich blood. As shown in Fig. 1, this obstruction is caused by atherosclerosis, whose development is a lifelong process. According to "response to injury" hypothesis of atherosclerosis, endothelial dysfunction is the first step in atherosclerosis [11]. Subsequently, monocytes gather at the site of the injury and in turn provoke an inflammatory immune response that causes further damage to arterial wall. Over time, low density lipoprotein (LDL) penetrates into arterial wall and is modified by oxidasis, then combining with the monocytes derived macrophages to form foam cell. Simultaneously, T lymphocytes, dendritic cells, mast cells and platelets can enter the intima of arterial wall through injured endothelial layer and induce the releasing of cytokines. With the participation of these cytokines such as matrix metalloproteinases (MMPs) and platelet-derived growth factors (PDGF), VSMCs can proliferate and migrate through intermediate lesion via the degradation of extracellular matrix components, thus promoting the formation of atherosclerosis plaque. Once plaque ruptures, some pieces of the plaque can travel through arteries until causing a blockage. Then, myocardial infarction happens and leads to dysfunction of cadiocytes. Finally, injured vascular and heart muscle lead to the occurrence of CHD.

In this section, we mainly introduce the functions of related cells in the formation of CHD, including ECs, VSMCs, T lymphocytes, dendritic cells, monocytes, macrophage, mast cells, platelets and cadiocytes.

2.1 *ECs*

ECs are inert barriers that separate flowing blood from underlying tissue. They play important roles in regulating hemostasis, cellular and nutrient trafficking. Under normal conditions, ECs are well aligned, tight junction with very low rates of death and permeable to some macromolecules such as LDL. ECs can produce numerous vasoactive factors, such as nitric oxide (NO), prostaglandin, endothelin (ET-1) and Ang Ⅱ. Vascular dysfunction due to endothelial cell injury alters these normal homeostatic properties. For example, the synthesis of NO is reduced, whilst the expression of vasoconstrictive molecules such as ET-1, is up-regulated [12, 13].

Hyperlipidemia, hypertension, hyperglycemia and smok-

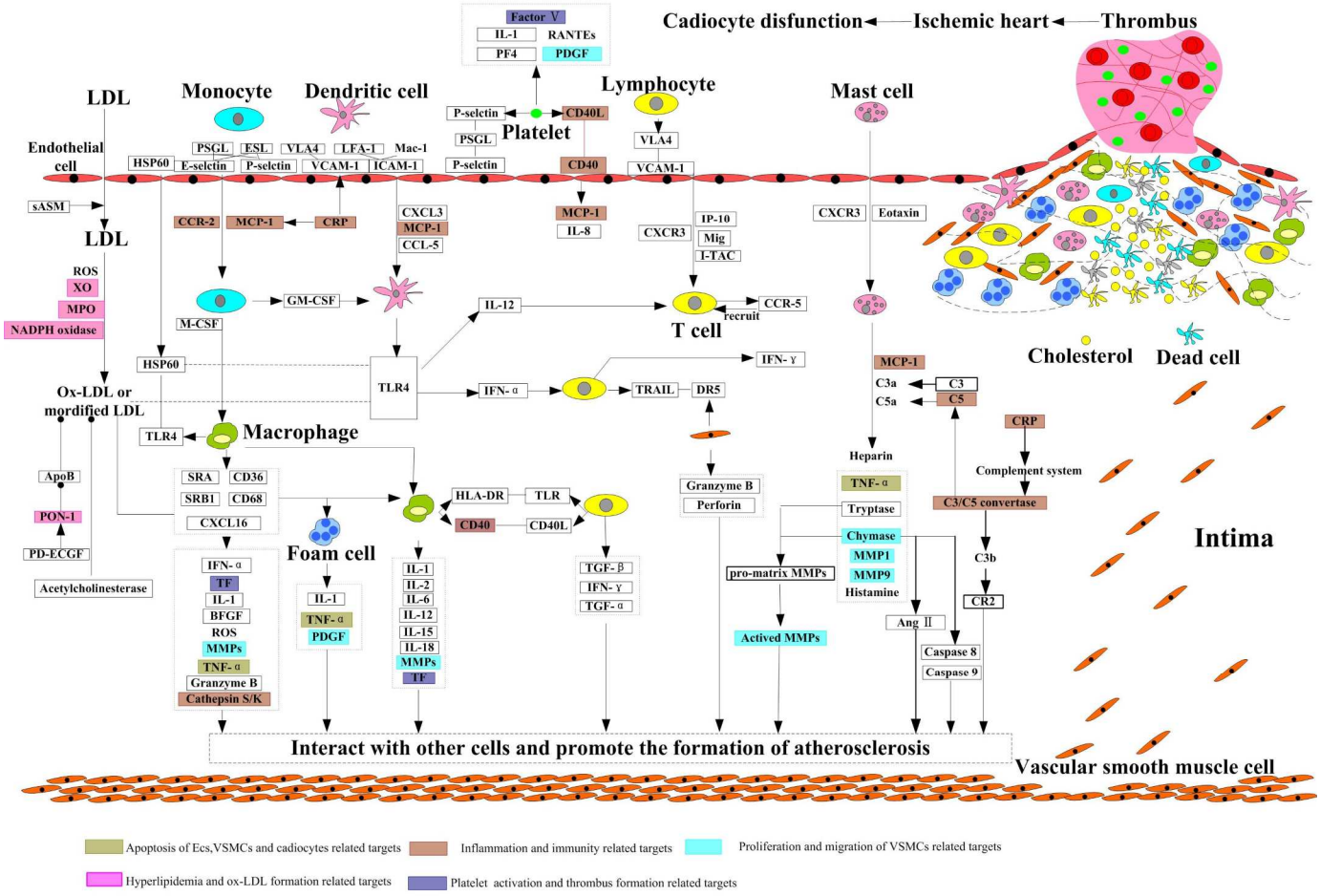

Fig. 1 Interaction of different cells in the formation of ischemic heart. All proteins were signed by rectangles. Drug targets were marked by different colors (the same as Table. 1) according to their different roles.

ing are main causes for ECs injury. As the increased permeability of ECs induced by injury, atherogenic matter LDL transmigrates through the endothelial layer and transforms into ox-LDL[14]. As shown in Fig. 2, once ox-LDL enters the intima, oxidized low-density lipoprotein receptor 1 (LOX) can be activated, thus inducing NF-Kb activation and leading to the up-regulation of adhesion molecules such as E-selectin, P-selectin, platelet-endothelial cell adhesion molecule (PECAM), intercellular adhesion molecule (ICAM) and chemotatic factors such as C-C motif chemokine 2 (MCP-1) and macrophage colony-stimulating factor 1 (M-CSF). In fact, except ox-LDL, HSP 60 and cytokines such as arachidonic acid (AA), protein geranylgeranyltransferase type-1 (GGTase), advanced glycation endoproducts (AGEs), immunoreactive fibronectin-γ (IFN-γ) and interleukin-1 (IL-1) can also promote ECs to secrete adhesion molecules and chemotatic factors. With the help of these adhesion molecules and chemotatic factors, the atherosclerotic cells like monocytes, lymphocytes, dendritic cells, mast cells and platelets begin to accumulate and enter intima, thus increasing the likelihood of plaque formation [14-16].

Apoptosis of ECs is an important event in ECs injury. As Fig. 2 shows, ox-LDL not only promotes the accumulation of atherogenic cells, but also participates in the apoptosis of ECs by activating caspase pathway. Oxidative stress and tumor necrosis factor-α(TNF-α) are also important factors leading to the apoptosis of ECs through regulating caspase pathway.

2.2 *VSMCs*

VSMCs are essential for vascular contraction and relaxation. They alter luminal diameter and enable blood vessels to maintain an appropriate blood pressure. The increased vas-

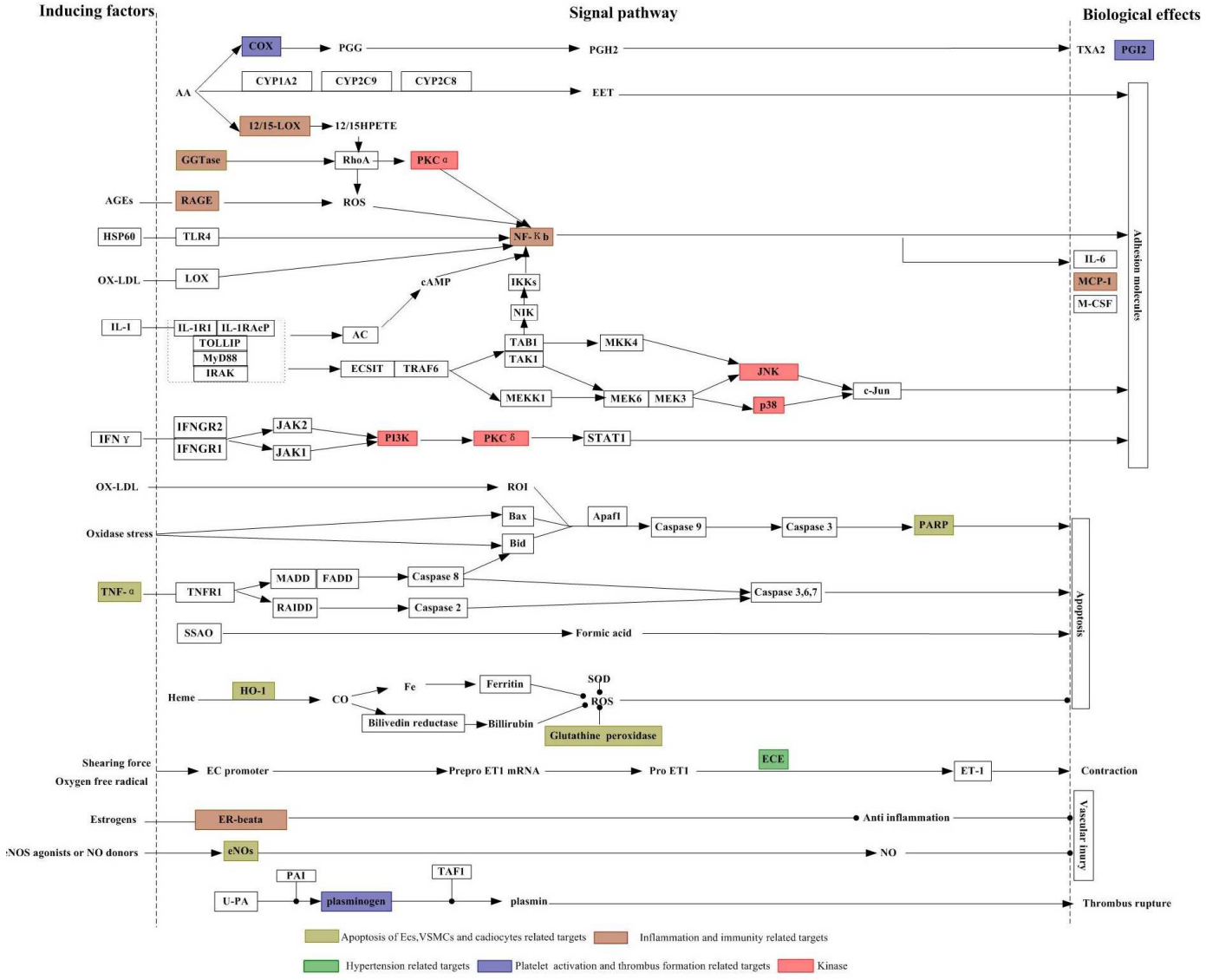

Fig. 2 The intracellular signal pathway of endothelial cell in CHD. All proteins were signed by rectangles. Drug targets were marked by different colors (the same as Table. 1) according to their different roles.

cular contractility, migration, proliferation and apoptosis of VSMCs are all important factors for the formation of atherosclerotic plaque.

(1) Contractility: The activation of renin-angiotensin system (RAS) is an important event for contractility of VSMCs. Once RAS is activated, the level of renin in blood is evaluated, thus promoting the production of Ang Ⅱ. By combinding with Ang Ⅱ receptors (AgtR1 and AgtR2), the contraction of vascular increase significantly (shown in Fig. 3) [17]. ET-1, the strongest vasoconstrictor peptide secreted by impaired ECs, also can stimulate contraction of VSMCs [18]. In addition, as shown in Fig. 3, 5-hydroxytryptamine (5 -HT) and AA metabolites such as hydroxy-eicosatetraenoic acids (HETEs) also make a contribution to the contraction of VSMCs.

(2) Migration and proliferation: As shown in Fig. 3, PDGF secreted by foam cells and activated platelets is the most important factor for migration and proliferation of VSMCs [19]. MMPs which can digest the extracellular matrix (ECM) in the intima also supply convenient condition for migration of VSMCs. In addition, urokinase-type plasminogen activator (U-PA) and leukotriene B4 receptor 1 (BLT1) also can aggravate the migration of VSMCs through activating focal adhesion kinase 1 (FAK) and up-regulating the production of MMPs (shown in Fig. 3)[20, 21].

In the aspect of proliferation of VSMCs, except PDGF, Ang Ⅱ and ET-1 are also important factors for the proliferation for VSMCs (shown in Fig. 3). In recent years, some studies demonstrated that urotensin Ⅱ can also inducing the proliferation of VSMCs [22, 23].

(3) Apoptosis: Proliferation and apoptosis of SMCs are coincidence events which not only contribute to vessel remodeling but also lead to destabilization of fibrous cap in arteriosclerotic lesions[24, 25]. Various stimuli, including oxidized lipoproteins, altered hemodynamic stress and free radicals, can precipitate macrophage and T lymphocytes to secrete apoptosis factors. TNF-a and IFN-γ are typical factors which contribute to the apoptosis of VSMCs and ECs [24] (shown in Fig. 2). T lymphocytes can also induce apoptosis of VSMCs via releasing perforin and granzyme B (shown in Fig. 1). In addition, Fas mediated apoptosis of VSMCs could be another important pathway as reported[26] (shown in Fig. 3).

2.3 *Monocytes and macrophages*

Monocytes can enter intima and differentiate into macrophages in the formation of atherogenesis. As shown in Fig. 1, with the continuing expression of adhesion molecules on injured ECs, monocytes are initially attracted to lesion-prone sites. The initial adhesion involves selectins, which mediate a rolling interaction, and is followed by firmer attachment by means of integrins. Adherent monocytes migrate into intima with the help of chemoattractant molecules MCP-1[4, 27]. After migrating into the subendothelial space, monocytes differentiate into activated macrophages via the existence of M-CSF[28]. Once differentiation is finished, scavenger receptors such as scavenger receptor class A (SRA) and platelet glycoprotein 4 (CD36) on surface of macrophages will phagocytose ox-LDL or other modified LDL, thus inducing the formation of foam cells and fatty streak in atherosclerosis.

Macrophages are considered to be major inflammatory mediators during atherosclerosis progression. As shown in Fig. 1 and Fig. 4, through combination of CD40 ligand with its receptor, macrophages can express amount of chemokines and cytokines such as MCP-1, RANTES, IL-1, IFN-γ, MMPs, TNF-α and tissue factor[29]. Once macrophages develop into foam cells, they also secret amount of cytokines. These factors continually augment inflammatory reaction in vessels and promote the development of atherosclerosis[5, 15] (Fig. 1). Except playing an important role in inflammation, macrophages also mediate the immunity reaction in atherosclerosis. Macrophages which contain phagotrophic ox-LDL particles act as antigen-presenting cells to T-cells [6] (Fig. 1).

Besides, a number of recent studies have demonstrated that macrophages also play an important role in reverse cholesterol transport [30, 31]. Ox-LDL can be decomposed into cholesterol and oxysterol in macrophages. Cholesterol is further modified into cholesterol ester with the help of acyl-CoA cholesterol acyl transferase (ACAT) and this leads to the formation of foam cells. Oxysterol can activate liver X receptor (LXR) in macrophages, thus promoting cholesterol efflux through apolipoprotein A-1 (ApoAI). By up-regulating ATP-binding cassette transporter 1 (ABCA1) and ApoAI, retinoic acid X activated peroxisome proliferator-activated receptor (PPAR) also participates in reverse transport of cholesterol in macrophages. In addition, nuclear receptor ROR, farnesoid X receptor (FXR) and ADP-ribosylation factor-related protein 1 (ARP1) in macrophages can also regulate the transportation of cholesterol through activating or inhibiting ApoAI.

2.4 *T lymphocytes*

T lymphocytes are the most important immune cells in atherosclerosis plaque. The trans-endothelial process of lymphocytes is similar to that of monocytes except using different chemoattractants. Known chemoattractants for T lymphocytes include inducible protein-10 (IP-10), monokine induced by IFN-γ (Mig) and IFN-inducible T-cell α-chemoattractant (I-TAC) [15, 32]. These chemokines bind to C-X-C chemokine receptor type 3 (CXCR3) which is expressed by T lymphocytes in atherosclerotic lesion and facilitate the migration of T lymphocytes (Fig.1).

Once residence in the arterial intima, T lymphocytes have chances to interact with antigen-presenting cells (APCs) such as macrophages. More and more studies demonstrated that CD40 ligand (CD40L) and its receptor CD40, which can be expressed in macrophages and T cells, play an important role in antigen presentation and autoimmunity as co-stimulatory factors [33, 34]. Except macrophages, VSMCs

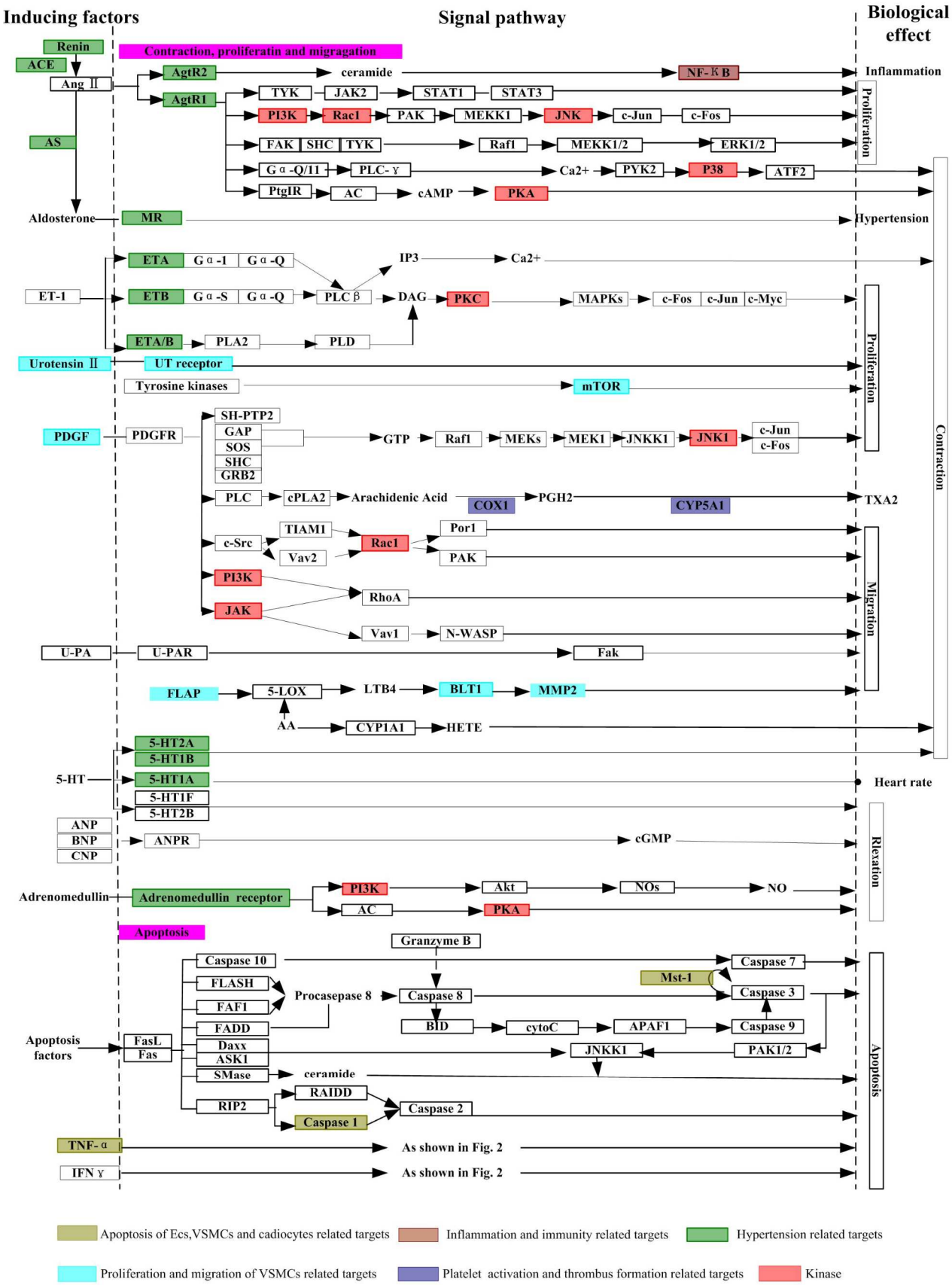

Fig. 3 The intracellular signal pathway of vascular smooth muscel cell in CHD. All proteins were signed by rectangles. Drug targets were marked by different colors (the same as Table. 1) according to their different roles.

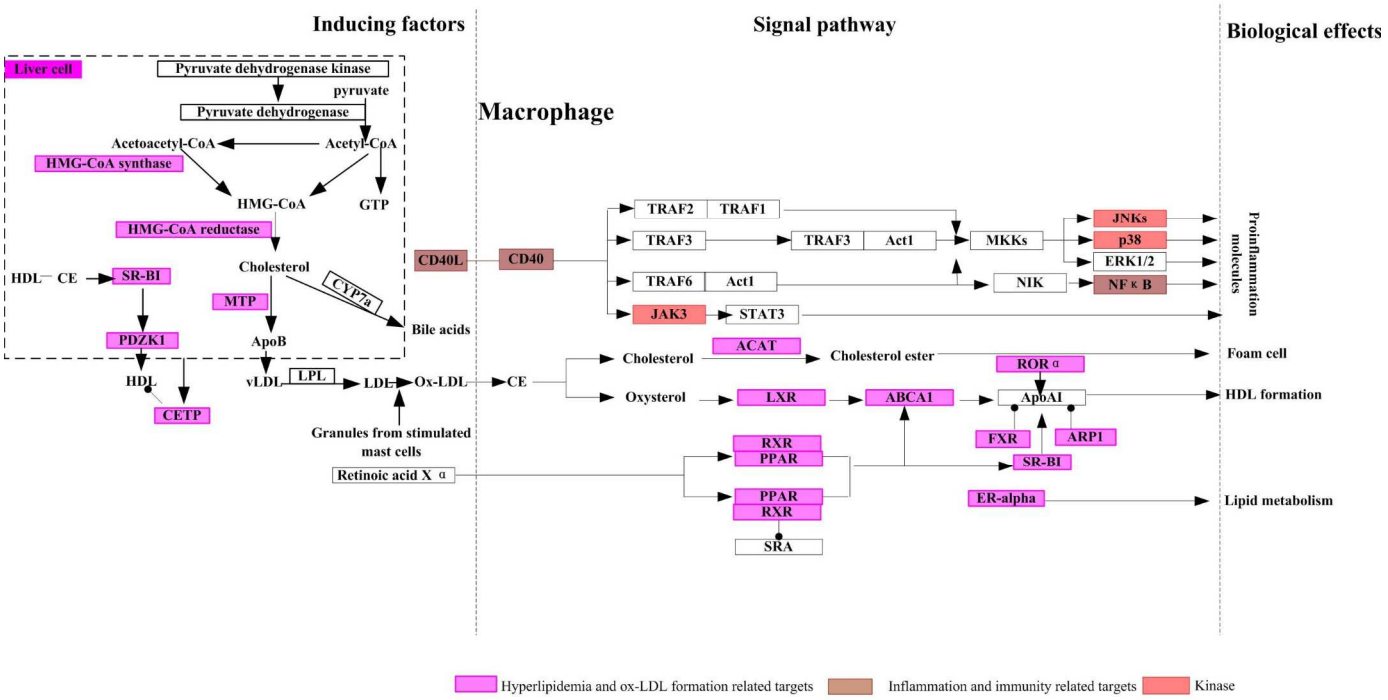

Fig. 4 The intracellular signal pathway of macrophage in CHD. All proteins were signed by rectangles. Drug targets were marked by different colors (the same as Table. 1) according to their different roles.

are another kind of APCs which can be recognized by T cells. By binding to a HLA class II histocompatibility antigen (DR5) which is expressed by VSMCs, T cells are activated, and then secrete granzyme B and perforin, both of which can induce apoptosis of VSMCs [8, 26](Fig.1). In some studies, oxidized LDL and heat-shock protein 60 (HSP60) also have been identified as antigens for T lymphocytes [35, 36].

As can be seen in Fig. 1, activated T cells also predominates the production of pro-inflammatory cytokines such as IFN-γ, TNF α and β and chemokines like C-C chemokine receptor type 5 (CCR5). These cytokines can augment the inflammatory and immune response [37].

2.5 *Mast cells*

Mast cells, an inflammatory cell type, contain highly enriched proteases, tryptase and chymase in intracellular granules. They have been found to participate in the inflammatory reaction of atherosclerotic lesions.

As shown in Figure 1, the trans-endothelial migration of mast cells is mediated by a chemoattractant named eotaxin which interacts with the chemokine receptor CXCR3 expressed on the surface of mast cells[32]. After entering intima and then being activated by complement system components such as complement C3a, complement C5a and chemokines such as MCP-1 [38, 39], mast cells become degranulation and release a number of inflammatory mediators including histamine, tryptase, chymase and a variety of cytokines, which can promote vascular inflammation, endothelial dysfunction and foam cell formation[40]. The subendothelial LDL can be modified by binding to the granule remnants from activated mast cells. These binding particles can be phagocytosed by macrophages more likely than LDL alone, thus promoting the formation of foam cells [41] (Fig. 4). A study has demonstrated that granules from stimulated mast cells can also degrade the capability of removing cholesterol from macrophages [42]. Therefore, mast cells not only promote LDL aggregation but also interfere with cholesterol removal, both of which contribute to foam cell formation.

Mast cells can also weaken the fibrous cap in different ways as follows (Fig. 1). (1) Activated mast cells may release MMPs, such as MMP-1 and MMP-9, both of which directly cause matrix degradation [43, 44]. (2) Secreted tryptase and chymase precipitate the pro- MMPs to form active MMPs [40, 45]. (3) Stimulated mast cells can express TNF-α which is able to enhance the apoptosis of VSMCs, macrophages and ECs, and subsequently weaken and rupture the atherosclerotic plaques [46]. (4) Chymase released from mast cells is reported to activate caspase-8 and caspase-9, two key effector molecules in apoptotic cascade[47].

2.6 *Dendritic cells*

DCs are also antigen-presenting cells with the unique ability to initiate a primary immune response by activating naive T lymphocytes. Though, DCs are typically localized in the subendothelial space as indigenous residents of healthy arteries, circulating DCs in blood can evade into injury sites with the help of chemokines and adhesion molecules in the progress of atherosclerosis[48]. As shown in Fig. 1, adhesion molecules such as P-selectin, E-selectin and VCAM-1 and

chemokines such as C-X-C motif chemokine 3 (CXCL3) and C-C motif chemokine 5 (CCL5) are all potential candidates for recruiting DCs to trans-endothelium[49, 50]. Granulocyte/macrophage colony-stimulating factor (GM-CSF), which may facilitate the transformation of trans-endothelial monocytes into DCs, is another factor to increase the number of DCs in atherosclerotic area [51].

Subendothelium DCs express toll like receptors (TLRs) to recognize dangerous signals and phagocytize antigens such as oxidized LDL and heat-shock proteins. Once finishing the process of phagocytosis, DCs become activated and produce vast amounts of cytokines such as IFN-α and interleukin-12 (IL-12). IFN-α can up-regulate the expression of the proapoptotic protein TRAIL on T lymphocytes thereby multiplying their ability to kill plaque resident cells [8, 52]. IL-12 can up-regulate the expression of chemokine receptor CCR5 on T lymphocytes, which in turn leads to the accumulation of T lymphocytes in the atherosclerotic plaque [53].

2.7 *Platelets*

Platelets play an important role in hemostatic process and thrombus formation, as well as in the inflammation reaction in atherosclerotic plaque.

After the injury of ECs, the endothelial cells' barrier is lost. Extracellular matrix leaks from intima and triggers the formation of a hemostatic thrombus. In this event, platelets participate in three successive and closely integrated biological process, i.e., adhesion, activation and aggregation [54] (Fig. 5).

(1) At impaired vascular lesions, extracellular matrix components like von Willebrand factor (vWF) and collagen are exposed to the blood. Platelets can detect these changes in blood circulation and adhere to collagen via the membrane adhesion receptor GPVI (platelet glycoprotein VI) which lead to further combination of vWF with integrin receptors GpIb-Ⅸ-Ⅴ (platelet glycoprotein IX-Ⅴ) and collagen with α2β1(integrin alpha-2) in platelets, thus resulting in the fast adhesion [55-58].

(2) Once adhesive receptors combine with their ligands on extracellular matrix components, the activation of platelets will start. This process can be further strengthened by thrombin, adenosine diphosphate (ADP), epinephrine and thromboxane A2 (TXA2), all of which are synthesized by stimulated platelets [54, 59-61].

(3) Aggregation is mediated by adhesive substrates bounding to membranes of activated platelets. Among adhesive substrates, activated GPIIb/IIIa (integrin beta-3/integrin alpha-IIb) is one of the most important factors contributing to the stable adhesion and recruiting more platelets [54, 62].

Platelets are also mediators of inflammation involved in the development of atherosclerosis. As shown in Fig. 1, (1) activated platelets can release P-selectin, which promote monocytes recruitment via platelet-monocyte interactions and deliver platelets' proinflammatory factors to monocytes; (2) activated platelet surface also express CD40L, which further binds to CD40 on the surface of ECs to up-regulate the expression of adhesion molecules and chemokines in ECs [63]; (3) Activated platelets can release amount of proinflammatory cytokines, chemokines, growth factors and blood coagulation factors, thus promoting leukocytes recruitment and proliferation of VSMCs 17 (Fig. 2).

2.8 *Cadiocytes*

Once obstruction happens in coronary vessels, myocardial ischemia takes place and disturbs the normal function of cadiocytes including dysfunction of myocardial energy me-

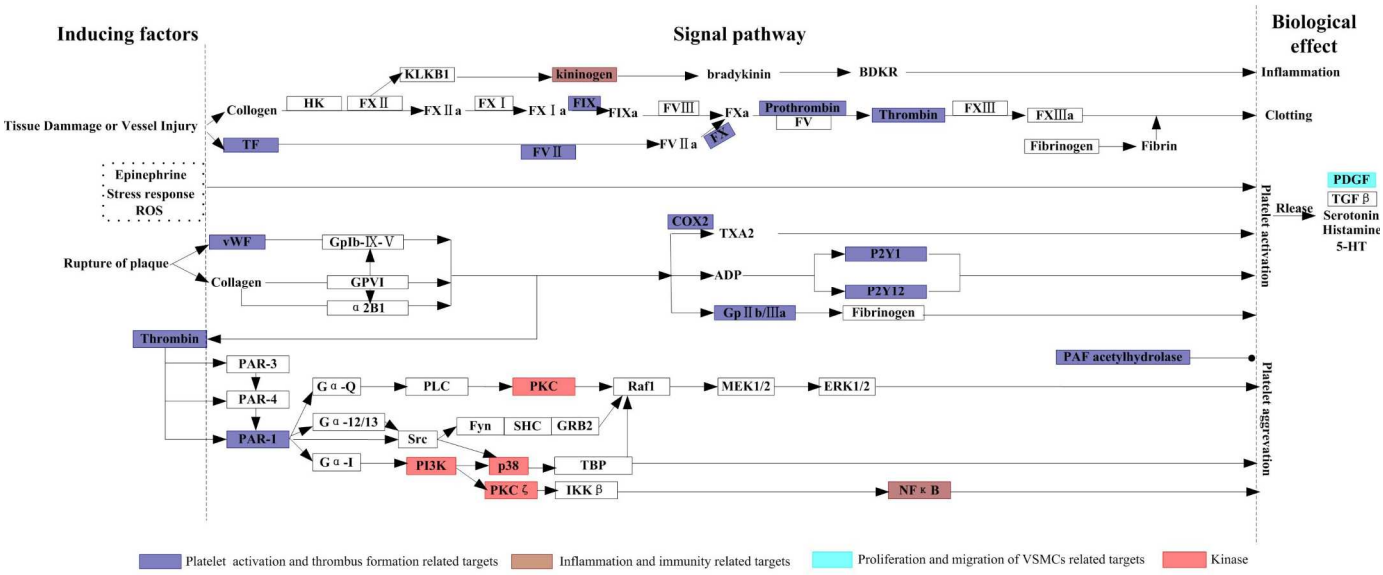

Fig. 5 The intracellular signal pathway of platelet in CHD. All proteins were signed by rectangles. Drug targets were marked by different colors (the same as Table. 1) according to their different roles.

tabolism, abnormal intracellular Ca2+ handling, cadiocytes hypertrophy and apoptosis.

(1) Dysfunction of energy metabolism

During ischemia, cardiac energy metabolism is dramatically altered, resulting in the occurring of fatty acid oxidation as the dominant source of oxidative metabolism at the expense of glucose oxidation [68]. As shown in Fig. 6, the proteins in AMPK (5'-AMP-activated protein kinase) pathway such as carnitine palmitoyl tranferase 1 (CPT-1), acetyl CoA carboxylase (ACC) and malonyl CoA decarboxylase (MCD) are important modifier factors in the energy metabolism of fatty acid [69].

Except with the imbalance of energy metabolism between fatty acid and glucose in ischemic heart, the other proteins related to energy such as F1F0 ATPase also become abnormal [70]. F1F0 ATPase is a critical enzyme to release ATP from catalytic F1 domain. But under ischemic conditions, this enzyme become an ATP hydrolase leading to an undesirable hydrolysis of ATP in ischemic heart [71, 72].

To overcome myocardial ischemia, endogenic reimbursement mechanism is activated. Hypoxia-inducible factor 1-alpha (HIF-α) may function as a master regulator of oxygen homeostasis [73, 74] By enhancing the transport of glucose, HIF-α increases the oxidation of pyruvate participating in the production of ATP in mitochondrion.

(2) Abnormal intracellular Ca2+ handling

Once heart ischemia happens, the concentration of noradrenaline/adrenaline, Ang Ⅱ, ET-1, dopamine, acetylcholine and histamine in circulation significantly increases. By binding to their receptors on cadiocytes, these factors induce abnormal intracellular Ca2+ handling. In cadiocytes, both calcium release channel ryanodine receptor (RyR) and sarcoplasmic reticulum Ca2+-ATPase (SERCA2) can mediate Ca2+ releasing into the sarcoplasmic reticulum, thus inducing the decrease of intracellular Ca2+ concentration. L-type Ca2+ channels (LTCC) is a Ca2+ inflow channel which may induce the increase of intracellular Ca2+ concentration [75, 76] (Fig.6). The dysfunction of these proteins will directly result in abnormal Ca2+ handling.

(3) Hypertrophy of cadiocytes

Hypertrophy is another significant pathological change as the result of ischemia. Elevated Ca2+ concentration is an important factor for cadiocytes hypertrophy. High levels of Ang Ⅱ and ET-1 after ischemia can seriously affect Ca2+ concentration in cadiocytes (Fig. 6). There are some other up -regulated cytokines contribute to cadiocytes hypertrophy. For example, both transforming growth factor beta-1 (TGF-β) and urotensin Ⅱ can combine with their receptors on the surface of cadiocytes and then induce hypertrophy (Fig. 6).

(4) Cell apoptosis in ischemic heart

Except that the dysfuction of energy metabolism and abnormal intracellular Ca2+ handling can induce the apoptosis of cadiocytes, some other factors can also contribute to this process. As Fig. 6 shows, with the help of monoamine oxidase, 5-HT can produce H2O2. H2O2 and another noxious substances reactive oxygen species (ROS) both can lead to DNA strand-breakage [77, 78]. Subsequently, poly(ADP-ribose) polymerase (PARP) induces inefficient cellular metabolic cycle and promote cadiocytes' death [79, 80].

On the other side, some endogenous factors such as thyroid hormone and adenosine are beneficial to cadiocytes in hypoxia condition. For example, adenosine is released by ischemic cadiocytes and subsequently reduces cellular injury and restores energetic homeostasis by binding to its receptors [81, 82]. The single pathway of adenosine and thyroid hormone are showed in Fig. 6.

3. Targets and corresponding medicines for CHD treatment

Proteins involved in the important CHD related pathways may be speculated as potential drug targets for CHD. Nowadays, more and more CHD targets have been identified and their corresponding medicines have received satisfactory effects for the treatment of CHD in clinic. These targets and their corresponding medicines are summarized in this section (Supplementary Table 2).

3.1 *Anti hyperlipidemia*

As the relationship between elevated plasma lipids and the development of atherosclerotic plaques has been well established, dyslipidemia has been considered as a major contributor to atherosclerosis-associated conditions such as CHD [83]. Nowadays, the most widely used medicine in clinic for anti hyperlipidemia is statins which is able to give a curative effect by inhibiting HMG-CoA reductase. As shown in Fig. 4, HMG-CoA reductase is an important enzyme for the formation of cholesterol. By inhibiting HMG-CoA reductase, the synthesis pathway of cholesterol can be blocked, thus decreasing the amount of LDL. Except statins, HMG-CoA synthase inhibitors, which is also in the pathway of cholesterol formation, is another important modifier for the down-regulation of LDL-c level [84] (Fig. 4). In addition, LDL-c can transform into ox-LDL in intima with the help of oxidases (Fig. 1). To decrease the effects induced by ox-LDL, some antioxidation medicines such as the inhibitors of xanthine oxidase (XO) [85, 86], NADPH oxidase [87] and myeloperoxidase (MPO) [88] have been discovered.

There are overwhelming evidences showing that a low plasma level of HDL is an important independent risk factor for CHD [83, 89]. Therapeutic intervention aimed at raising HDL has become a strategy increasingly adopted by Adult Treatment Panel III (ATP III) guidelines [90]. Niacin which stimulates ABCA1 to elevate the level of HDL has been widely used in clinic [91]. From pathways of HDL formation showed in Fig. 4, it can be seen that some other related proteins may be identified as potential drug targets. For example, several evidences have demonstrated that irritating the activity of LXR [30,92], PPAR [91,93] and scavenger receptor class B member 1 (SR-BI) [94] or inhibiting the activity of FXR and ARP1 [95, 96] can increase the level of HDL and

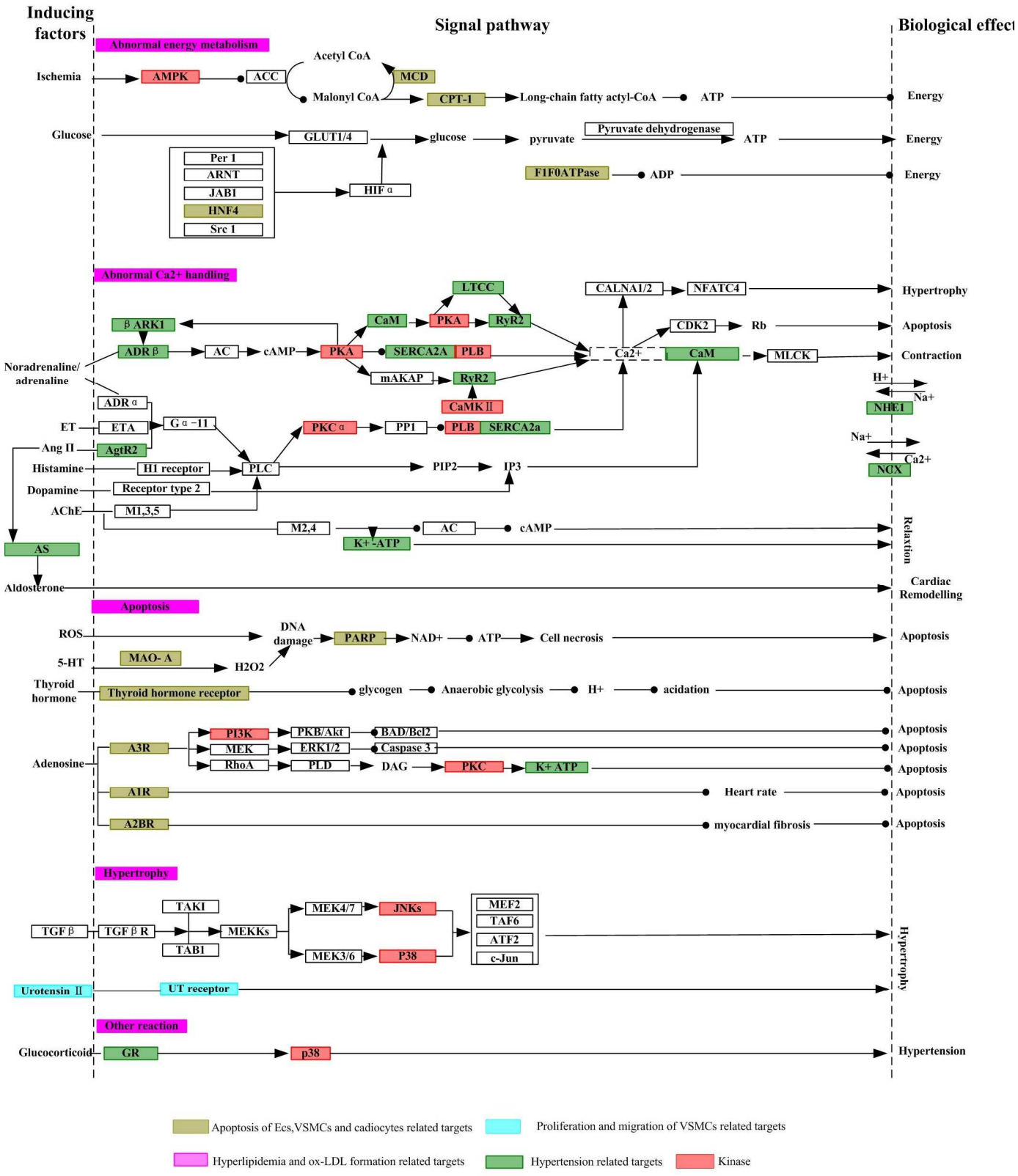

Fig. 6 The intracellular signal pathway of cadiocyte in CHD. All proteins were signed by rectangles. Drug targets were marked by different colors (the same as Table. 1) according to their different roles.

decrease the incidence of CHD obviously.

Decreasing the formation of cholesterol is another effective method for anti dyslipidemia. Bile acid sequestrants cholestyramine and colestipol promote the bile acid transformation from cholesterol, thus decreasing the LDL level and the morbidity of CHD [97]. The application of bile acid sequestrant in dyslipidemia has been recommended in ATP Ⅲ. Cholesterol absorption inhibitor ezetimibe is another important anti hyperlipidemia medicine and widely used in clinic. By inhibiting the absorption of cholesterol, ezetimibe can efficiently control the level of LDL[83]. In addition, estrogen or hormone replacement therapy has been demonstrated their effects in favorable changes in lipid profiles, but its therapeutic effects are skeptical now because of the increased risk of thromboembolic events [98, 99].

3.2 *Anti hypertension*

Hypertension is another major risk factor involved in CHD. In ESH-ESC practice guidelines, five major classes of antihypertensive agents including ACE-inhibitors, angiotensin receptor blockers, ß- adrenoreceptor inhibitors, calcium antagonists and thiazide diuretics are recommended for the initiation and maintenance of anti hypertensive treatment [100].

In the development of atherosclerosis and ischemic heart formation, RAS and sympathetic nervous system (SNS) are excited [101], thus increasing contractility of heart muscle and vascular smooth muscle and leading to high blood pressure. Inhibiting the activated RAS and SNS is an effective way to restrain the hemodynamic disturbance. Proteins playing important roles in the RAS pathway, such as ACE, AgtR and rennin, have been identified as drug targets (Fig. 3) and their corresponding medicines have received satisfactory effects in the treatment of hypertension [102-104]. Beta-adrenergic receptor kinase 1 (βAR kinase) and β-adrenoceptor (ADRβ) in SNS pathway also have been identified as drug targets for inhibiting the contraction of cardiac muscle. ADRβantagonists also have been extensively adopted in clinic to inhibit the activity of SNS [105, 106].

As can be seen in Fig 6, inhibiting the elevated concentration of intracellular Ca2+ will be another effective method to decrease the contractility of heart muscle. Several important proteins involved in this biological process have been identified as drug targets, such as LTCC (L-type calcium channel), calmodulin (CaM), RyR2, SERCA2a, sodium/hydrogen exchanger 1 (NHE1) and NCX (sodium/calcium exchanger 1) [75,107-111]. The representative Ca2+ handling medicines have been shown in Supplementary Table 1.

Except regulating drug targets directly related to the pathways of hypertension, using diuretics to down-regulate high blood pressure indirectly is another effective method. Diuretics can inhibit the reabsorption of sodium at different segments of the renal tubular system. Through their effects on sodium and water balance, diuretics decrease ventricular stroke volume and cardiac output, finally leading to a fall in arterial pressure. Diuretics have been used in the management of hypertension for approximately ninety years, and it is still widely applied in clinic now[112, 113].

In addition, ET-1 secreted by ECs after endothelial injury also induce the dysfunction of contractility [114] (Fig. 1 and Fig. 3). Endothelin receptor antagonists such as bosentan and tezosenta have been applied in clinic and received satisfied effects [115, 116]. Endothelin converting enzyme (ECE), a key enzyme for ET-1 formation (Fig. 2), is also considered as a potential drug target [117, 118].

3.3 *Anti platelet treatment*

Platelets play an important role in thrombus formation as well as in inflammatory reaction. American College of Chest Physicians (ACCP) evidence-based clinical practice guidelines (8th Edition) has supplied the intimate therapeutic methods for anti platelet in patients with CHD [119]. Alteplase, aspirin, clopidogrel, abciximab and vitamin K antagonist are main recommended medicines for CHD related condition. By regulating the different pathways in the process of platelet activation and aggravation (Fig. 5), these medicines receive therapeutic effects in clinic.

As shown in Fig. 5 and Supplementary Table 1, aspirin is the most representative anti platelet medicine through inhibiting cycloxygenase. Clopidogrel and abciximab block the activation of platelet through inhibiting P2Y12 receptor and GP IIb/IIIa, respectively. If patients have symptom of myocardial infarction, alteplase (plasminogen agonist) or vitamin K antagonist (thrombin/Factor II, Fator Ⅶ, Factor Ⅸ, and Factor Ⅹ inhibitor) is available for thrombolysis therapy. In addition, some other medicines such as platelet-activating factor (PAF) acetylhydrolase agonists [120], proteinase activated receptor 1 (PAR-1) inhibitors [121] were also developed and some of them have been used in clinic.

3.4 *Inhibiting inflammatory and immune reaction*

As can be seen in Fig. 1, inflammatory and immune reaction coexisted in all stages of atherosclerosis. The development of inhibitors for inflammatory and immune reaction will be beneficial for the treatment of CHD. Some chemotatic factors such as MCP-1 and CCR2 have been identified as potential drug targets for inhibiting the inflammation in atherosclerosis. In immune reaction of atherosclerosis, complement system is activated. Complement C3/C5 convertase and complement C5 have been identified as drug targets and their corresponding medicines have been used in clinic[122].

Except the targets in extracellular, there are a lot of important intracellular targets contributing for the inflammation and immunity, such as NF-Kb [123] and RAGE [124, 125]. For example, as shown in Fig. 1, RAGEs bind the circulating AGEs, resulting in the generation of reactive oxygen species (ROS) and further activation of NF-κB. To decrease the damage induced by AGEs, blocking the combination of AGE and RAGE becomes a new way to control CHD. RAGE

antagonist like ALT711 have showed their therapeutic effectiveness in clinic [126, 127]. Some other inflammation related drug targets and their representative medicines have been shown in Table. 1.

3.5 *Inhibiting the apoptosis of ECs, VSMCs and cadiocytes*

The apoptosis of ECs leads to the loss of integrity of endothelial monolayer and facilitates the migration and deposition of lipids or monocytes, thus propagating the atherosclerotic plague development. The particles of apoptosis VSMCs not only are major components in atherosclerotic plaque but also contribute to destabilize the plaque. The apoptosis of cadiocytes, which is induced by heart ischemia, lead to the development of myocardial damage. Therefore, the treatment of apoptosis of ECs, VSMCs and cadiocytes are important ways to inhibit the process of CHD.

As inhibiting the activities of glutathione peroxidase and heme oxygenase can decrease the formation of ROS, thus avoiding injury of ECs, these proteins are considered as potential targets for the prevention of CHD in the future [128-130]. In addition, as eNOS agonists or NO donors such as S-nitrosothiols [131, 132], NONOates [133, 134] and tetrahydrobiopterin [135] can participate in NO formation, some of them have been used in clinic. As shown in Fig.2 and 3, TNF -α and some proteins in caspase pathway play a central role in the apoptosis of ECs and VSMCs, the inhibitors of caspases and TNFα have been under investigated and attained therapeutic effects through many years' clinic trails [136-138].

As Fig. 6 shows, proteins related to cadiocytes apoptosis have been summarized. Some of them have been identified as drug targets, such as adenosine receptor, PARP and monoamine oxidase A (MAO-A) [139-141]. In addition, Thyroid hormone can decrease the anaerobic glycolysis and inhibit the acidosis and apoptosis of cadiocytes. In clinic, the homolog of thyroid hormone such as DIPTA, GC-1 and its agonist desethylamiodarone have exhibited their therapeutic effects for the treatment of CHD [142-144].

Regulating proteins related to energy metabolism of cadiocytes is another way to restrain the apoptosis of cadiocytes. As Fig. 6 shows, CPT-1 and MCD, two important enzymes related to metabolism of fatty acid, have been identified as drug targets [145-147]. In addition, the activation of F1F0 ATP synthase can elevate content of ATP in myocardium, decrease energy consume and protect ischemic heart [70, 148, 149]. So F1F0 ATPase maybe a new potential drug target for controlling CHD.

Other drug targets and their representative medicines for inhibiting apoptosis of ECs, VSMCs and cadiocytes were listed in Table. 1.

3.6 *Anti migration and proliferation of VSMCs*

The proliferation and migration of VSMCs play an important role in the formation of atherosclerotic plaque. Factors like PDGF and MMPs are the most important cytokines which can directly induce proliferation and migration of VSMCs (Fig.1 and Fig. 3), while their antagonists such as trapidil (an antagonist of PDGF) [107] and doxycycline (an inhibitor of MMPs) [150] have been used as anti atherosclerotic medicines. Additionally, antagonists of serine/threonine-protein kinase mTOR (mTOR) [151, 152], arachidonate 5-lipoxygenase-activating protein (FLAP) [153] and urotensin-2 receptor (UT receptor) [154] also can inhibit migration and proliferation of VSMCs (Fig. 3). Other drug targets and their representative medicines for inhibiting migration and proliferation of VSMCs were listed in Table. 1.

3.7 *Inhibiting the activity of CHD related kinases*

Protein kinases play connective roles to transmit external stimuli to evoke intracellular biochemical reaction. Theoretically, they have comprehensive ability to regulate intracellular pathway and obtain desirable clinic effects. Kinases like protein kinase A (PKA), protein kinase C (PKC), phosphoinositide 3-kinase (PI3K), mitogen-activated protein kinase (JNK) and tyrosine protein kinase JAK (JAK) are the most common kinases related to CHD. Some kinases' inhibitors such as ruboxistaurin (a PKC-β inhibitor) [155] and wortmannin (a PI3K inhibitor) [156, 157] have been applied in clinic for the treatment of CHD. Though different therapeutic effects were received in clinic trials, the method searching for inhibitors of kinases to treat CHD still become a hot spot in drug discovery.

4. Medicine combination therapy for CHD

With the accumulation of experience in medicine application for the treatment of CHD, it has been found that monotherapy using only one compound can't make a satisfactory result because of complex pathogenesis of CHD. To overcome shortcomings of monotherapy, medicine combination therapy was adopted. Clinic studies have demonstrated that polytherapy using two or more medicines can obviously ameliorate therapeutic effects and elevate patients' quality of life.

4.1 *Combination therapy for anti hyperlipidemia*

Ezetimibe (a cholesterol absorption inhibitor) and statins (HMG-CoA reductase inhibitors) are both used to decrease LDL level. Coadministration offers an effective treatment option for patients with hypercholesterolemia, compared to statins monotherapy [158-160]. Colestipol, a bile acid sequestrant, is also used in combination therapy with statins. Trials have demonstrated that treatment with lovastatin and colestipol for 2-2.5 years slowed or reversed the progression of atherosclerosis, as assessed by angiography [161].

Combination therapy which can simultaneously decrease LDL level and elevate HDL level also used in clinic [162-164]. Combined therapy by statins and niacin (ABCA1 ago-

nist), which is recommended in ATP Ⅲ guidelines, provides an option to help patients to attain their low-density lipoprotein cholesterol (LDL-C) goals and HDL goals [165, 166]. Monontherapy of probucol (SR-BI agonist) or fibrate (PPAR -α agonists) can raise HDL level. Actually, in clinic, the combination of probucol or fibrate with statins is used more often for the treatment of angina in CHD patients with hypercholesterolemia.

4.2. *Combination therapy for anti hypertension*

Diuretic, β-ADR antagonist, calcium antagonist, ACE inhibitor and Ang Ⅱ receptor inhibitor are five mainly used medicines for anti-hypertension in clinic. According to 2007 ESH-ESC Practice Guidelines, any two categories can be simultaneously administrated [100].

ACE inhibitors are the first line medicines for the treatment of hypertension in the guideline of ESH/ESC. By coadministration with other anti-hypertension medicines, ACE inhibitors can receive a better therapeutic effect with lower toxicity [167-169]. The combined therapy with a diuretic and a β-ADR antagonist is also important in anti-hypertension. Their combination has been shown highly effective in reducing cardiovascular events in both diabetic and nondiabetic patients [170, 171]. The combination medicine including these two medicines has been proved by FDA as the first line anti-hypertension medicine. Except coadministration with an ACE inhibitor, Ca2+ channel antagonists can also simultaneously administrate with a β-ADR antagonist, an angiotensin receptor inhibitor or a diuretic. All the combined therapies have been demonstrated their therapeutic effects in clinic [172-174].

4.3. *Combination therapy for anti platelet*

Combination therapy for anti platelet in CHD treatment has been widely adopted in ACCP-8 guidelines [119]. Aspirin is a representative medicine for anti platelet therapy. It is usually coadmintrated with other anti platelet medicines such as clopidogrel (P2Y12 receptor antagonist) to control the development of CHD in clinic [175, 176]. On the other side, ATP Ⅲ guidelines also recommend the combination therapy of aspirin and statins for CHD patients to reduce prothrombotic state [90, 177, 178]. Five major clinical studies have demonstrated that the combination of pravastatin and aspirin was significantly more effective than each agent alone in reducing the relative risk of key cardiovascular endpoints including MI and ischemic stroke [158].

4.4. *Other combination therapy in CHD treatment*

High blood pressure combined with high cholesterol level constitutes a serious risk for CHD. Hence, decreasing LDL-C level and high blood pressure through coadministration of an antihypertensive and a statin has potential benefit in management of CHD [179, 180]. It was found that coadministration of valsartan and simvastatin was well tolerated and associated with significant reductions from baseline in blood pressure and LDL-C [181].

In the end stage of CHD, heart failure is a common event. To reverse this pathological processing, many combination therapies have been recommended. Published guidelines for the treatment of heart failure support the combination therapy by using an ACE inhibitor with a β-ADR inhibitor [182-184].

To simplify the effective treatment of CHD, pollypill or fixed dose combinations (FDCs) have attracted the manufactures' favor [185]. In recent years, more and more FDCs such as Coveram (containing perindopril and amlodipine), Caduet (containing amlodipine and atorvastatin) and Vytorin (containing ezetimibe and simvastatin) have appeared on the market for the treatment of CHD [186-189]. Trials of a polypill containing a statin, three blood pressure lowering agents, aspirin and folic acid have been undertaken and shown exciting result in decreasing the incidence of CVDs by more than 80% after phase Π clinical trial [190, 191].

5. Conclusion

CHD is a chronic and multifactorial disease. As hundreds of complex signal pathways containing in the CHD formation, it is important to construct biological network and protein database about CHD. In this review, we not only compiled CHD related signal pathways and protein database, but also provide a comprehensive knowledge of drug targets and their application in clinic for the treatment of CHD. As protein database include potential drug targets for the treatment of CHD, it may convenient the drug discovery in the future. With the development of drug discovery, it can be anticipated that more and more efficiently medicinal solutions would be applied in clinic for the treatment of CHD.

6. Supplementary material

Supplementary data and information is available at: http://www.jiomics.com/index.php/jio/rt/suppFiles/105/0

Supplementary material includes: Supplementary Table 1 showing CHD related targets and their corresponding medicines ; Supplementary Table 2 listing 413 CHD proteins participating in multiple intracellular and extracellular signal pathways.

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