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# Inflammation and Genetics of Inflammation in Cardiovascular Diseases

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## 1. Introduction

Inflammation is a complex of defensive mechanisms reacting to the entry of harmful agents to the organism or cells in order to eliminate or at least to dilute the agent, repair damaged cells or tissue and restore homeostasis. From this definition it is clear, that inflammation does not accompany only infectious diseases but also others, causing cell, tissue or organ injury and serves primarily defensively (Table 1). An exaggerated, chronic long lasting or non-adequately regulated inflammatory response could be the cause of adverse reactions and could lead to pathology (Bucova, 2002b).

Inflammation plays an important role also in the etiology of ischemic heart disease (IHD), myocardial infarction (MI), angina pectoris (AP) and hypertension, however, its mechanism in various stages of pathological process is not well understood (Bucova et al., 2008a; Itoh et al., 2007; Kuka et al., 2010; Li, 2005; Pickering et al., 2007, Ross 1999). If the cause of IHD is atherosclerosis or other, it is accompanied by inflammation. Various types of inflammatory cells, cytokines, chemokines and other soluble factors were confirmed to be involved in this process. (Armstrong et al 2006; Aukrust et al., 2001; Brunetti et al., 2006; Bucova et al., 2008a; Ferencik et al., 2007).

- |   |
|---|
| <ol style="list-style-type: none"><li>1. Infectious - bacteria, fungi, viruses</li><li>2. Mechanical – scratching, cutting</li><li>3. Physical – burning, radiation</li><li>4. Allergic</li><li>5. Autoimmune</li><li>6. Atherosclerosis and cardiovascular diseases</li><li>7. Cancer</li><li>8. Nutritional disorders - hypoxia, lack of proteins, vitamins, etc.</li><li>9. Other causes</li></ol> |
|---|

Table 1. Inflammation and its induction agents

## 2. Immune mechanisms and cardiovascular diseases

**Inflammation** and **immune system activation** are strongly involved in the pathogenesis of atherosclerosis and cardiovascular diseases. Atherosclerosis is now considered to be a

chronic inflammatory disease of the arterial wall where both innate and adaptive immune mechanisms contribute to disease initiation and progression (Table 2).

Non-specific innate immunity	Specific adaptive immunity	Autoimmunity
1. CELLULAR	1. CELLULAR	1. CELLULAR
monocytes, macrophages, neutrophils, eosinophils, NK- cells	T helper cells (Th1, Th2, Th17) T cytotoxic cells (Tc) regulatory T cells (innate and induced)	Tc - lymphocytes
2. HUMORAL	2. HUMORAL	2. HUMORAL
cytokines TNF- $\alpha$ , IL-1, IL-6, chemokines (MCP-1/CCL2, CXCL16, ...) MMP-9, complement, acute phase proteins, histamin, chymase, tryptase, endogenous vasoconstrictors, elastase, ...	cytokines IFN- $\gamma$ , IL-12, IL-2, IL-4, IL-10, IL-17, IL-33, TGF- $\beta$	specific antibodies
3. RECEPTORS (non-specific)	3. Receptors (specific)	
PRR (CD14, TLR, Dectins, TREM-1, RAGE, CR1, CR3, CR4, CRP ...) Fc $\gamma$ R, scavenger receptors	T cell receptor (TCR) B cell receptor (BCR)	
4. MECHANISMS	4. MECHANISMS	
inflammation, innate imunity (phagocytosis, complement activation, ...) antigen presentation, potentiation of adaptive immunity	polarization of T cells, activation of specific immunity	antibodies against self, damaged or changed antigens (oxLDL, HSP, ...)

Legend: NK- natural killer, TNF – tumor necrosis factor, IL-1 – interleukin 1, MCP-1 – macrophage chemotactic protein, PRR – pattern recognition receptors, TLR – toll like receptors, TREM-1 (triggering receptor expressed on myelocytes, RAGE – receptor for advanced glycation end product, CR1, CR3, CR4 – complement receptors, Fc $\gamma$ R – receptor for Fc fragment of immunoglobulins, IFN- $\gamma$  - interferon - gama, TGF- $\beta$  - transforming growth factor beta, oxLDL – oxidized low density lipoprotein, HSP – heat shock protein.

Table 2. Main immune mechanims involved in cardiovascular diseases

To main players of the **innate immune system** belong macrophages, mastocytes and from soluble factors complement components, pro-inflammatory cytokines (tumor necrosis factor (TNF), interleukin-1 (IL-1) and IL-6, chemokines (monocyte chemoattractant protein - MCP-1/CCL2) and acute phase proteins, mainly C-reactive protein (CRP), serum albumin A (SAA) and pentraxins (PTX).

**Adaptive immune mechanisms** involved in the pathogenesis of cardiovascular diseases are represented predominantly by T helper 1 type (Th1), Th2 and Th17 lymphocytes and

immune mechanisms associated with them (Chen et al., 2010; Mostafazadeh et al., 2011) (Table 2). Th1 immunity insures defence against intracellular pathogenic microorganisms, viruses, fungi and tumors, Th2 against extracellular pathogenic microorganisms and helminths and Th17 against extracellular bacterial infection and fungal infection. Exaggerated response of any of mentioned type of immunity contributes to the pathogenesis of various autoimmune inflammatory diseases (Fouser et al., 2008; Mucida et al., 2010; Quian et al., 2010). Cytokines activating these cells and/or produced by these cells and regulating the activity of these cells play a great role in development of atherosclerosis and cardiovascular diseases. The array of cytokines involved in pathogenesis of atherosclerosis is similar to those used by immune effector cells to kill foreign pathogens and damaged or diseased host cells. These are mainly IL-2, interferon-gama (IFN- $\gamma$ ), IL-10, IL-4, IL-17, IL-33 and transforming growth factor-beta (TGF- $\beta$ ) (Chen et al., 2010; Hansson et al., 2005). Regulatory T cells – both innate and induced, controlling the activity of helper T cells are other important components of adaptive immunity (Cheng et al., 2008; George, 2008).

Macrophages belonging to non-specific innate immune mechanisms amplify the adaptive immune response as antigen presenting cells that after having ingested and processed the foreign particle present an immunogenic fragment from it to naive Th0 lymphocytes and start and shift the immune response to the right direction.

**Autoimmune response** to at least two major autoantigens – oxidized lipoproteins (oxLDL) and heat shock proteins (HSPs) also potentiate inflammation. Namely, HSP60, an endogenous molecule with a chaperone activity, normally located in the mitochondria can be translocated into the cell membrane in response to stress stimuli. It can be released also by stressed or injured cells but also by activated monocytes and macrophages. HSPs in host can likewise be derived from microorganisms during infection, e.g. by *Helicobacter pylori*.

## 2.1 The innate and adaptive immunity

The innate immune response starts non-specifically as an inflammatory response that develops after pattern recognition receptors (PRR) at the surface of our immune cells (macrophages, dendritic cells, ...) recognize common molecular features originating either from microorganisms - pathogen associated molecular patterns (PAMPs), or from our own body, e.g. from damaged cells – damage associated molecular patterns (DAMPs) (Fig. 1, Table 3). Both PAMPs and DAMPs represent to immune system signals of threatening and bind these molecular patterns by PRR receptors – immune sensors of non-specific innate immunity. To these endogenous DAMPs called also alarmins belong both newly formed (HSPs, heat shock proteins), altered and modified endogenous antigens (oxLDL, oxidized low density lipoprotein cholesterol), or substances released from damaged or necrotic cells. The binding of any PAMPs and DAMPs to concrete PRR results in signal transduction, activation of transcription factors and production of early pro-inflammatory cytokines (TNF- $\alpha$ , IL-1 and IL-6) and chemokines from immune and injured endothelial cells (Chen et al., 2010; Eldfeldt et al., 2002; Ferencik, 2007; Miyake, 2007).

From this point of view the inflammatory response could be triggered directly by infectious but also by some sterile non-infectious stimuli. To the most intensively studied PRR with the involvement in the process of atherosclerosis belong toll like receptors TLR4 and TLR2, CD14 receptor and RAGE (receptor for advanced glycation end products) (Bierhaus et al., 2006; Bucova, 2006; Park et al., 2004).

The expression of adhesive molecules on both endothelial cells and leukocytes increases, chemokines attract monocytes into the vessel wall where they differentiate into

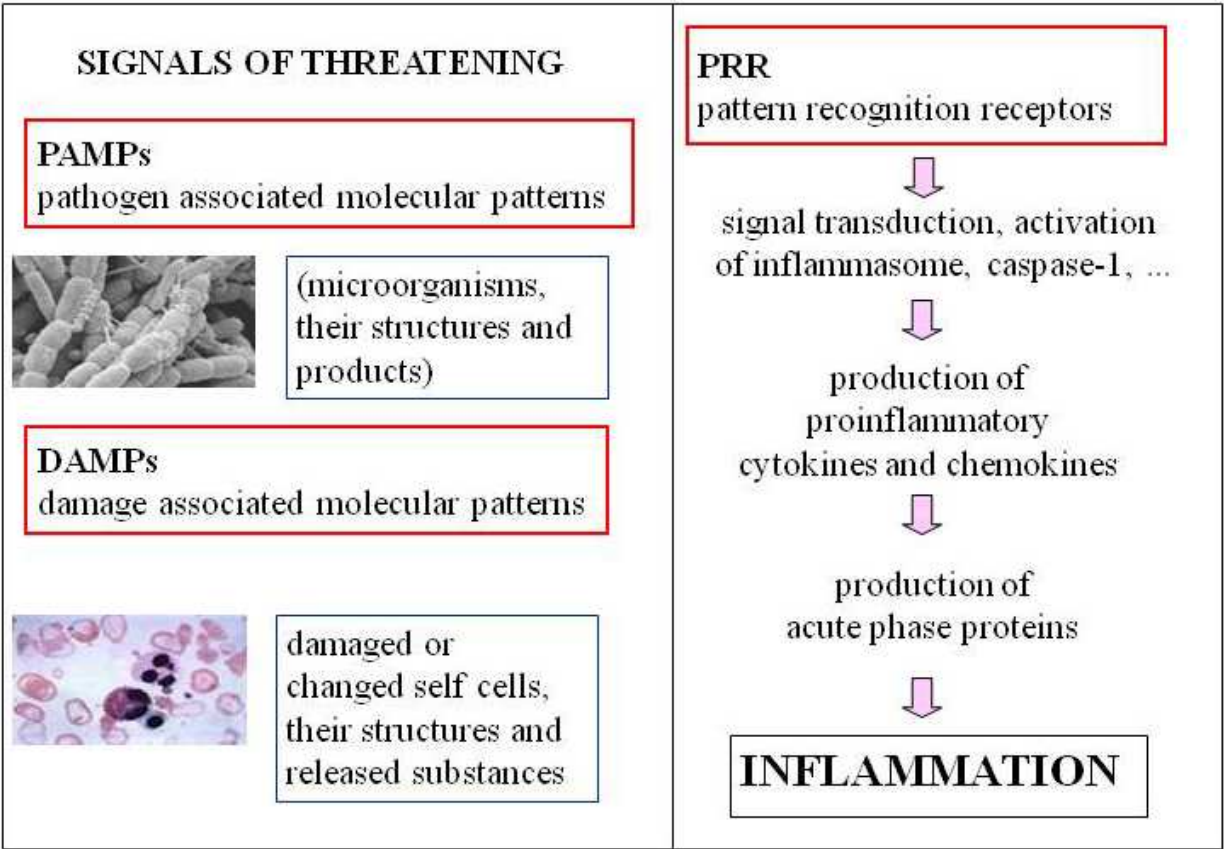


Fig. 1. Infectious and non-infectious inflammation induced by binding exogenous PAMPs and endogenous DAMPs by PRR.

PAMPs (pathogen associated molecular patterns) - microorganisms and their products	DAMPs (damage associated molecular patterns) - damaged or changed self cells and structures, and their products
lipopolysaccharide, peptidoglycan, lipoteichoic acid, lipoarabinomannan, flagelin, zymozan, ssRNA, dsRNA, CpG motifs of DNA, ...	hyaluronic acid, heparan sulfat, extra-domene A of fibronectin, HSP 60, HSP 70, uric acid (crystallic form), HMGB1, IL-33, fibrinogen, hyperglycaemia, hyperkaliemia, ....

Legend: ssRNA – single stranded ribonucleic acid, dsRNA – double stranded ribonucleic acid, DNA – deoxyribonucleic acid, HSP 60 – heat shock protein 60, HMGB1 – high mobility group box 1 protein, IL-33 – interleukin 33

Table 3. Some of the most important PAMPs and DAMPs

macrophages, ingest particles of oxLDL and transform into foam cells. Other substance with strong pro-inflammatory activity that serves also as alarmin or inflammatory mediator of tissue injury is high mobility group box 1 protein (HMGB1). HMGB1 is released both from injured endothelial cells and activated monocytes and macrophages, the next source of this protein are necrotic cells (Chang et al., 2011; Yang et al., 2010).



Released pro-inflammatory cytokines enhance the production of acute phase proteins in the liver and aggravate the inflammation. The pivotal transcription factor involved in the induction of specific pro-inflammatory genes is NF-κB (Barnes & Karin, 1997). Its activation might also represent a mechanism by which CRP amplifies and perpetuates the inflammatory response (Liuzzo et al., 2007) (Fig.1).

Inflammatory process in endothelial cell wall goes along with the activation of adaptive T cell immunity. Macrophages as antigen presenting cells present exogenous or endogenous antigens to naïve helper T cells (Th0), cells of the specific adaptive immunity. After naïve Th0 cells recognize the antigen (oxLDL, HSPs, components of microorganisms, ...), they differentiate into T helper type 1 (Th1) cells that produce interferon-gamma (IFN-γ), the main Th1 type cytokine (Bucova, 2002a; Chen et al, 2010) (Fig. 2, Table 2). IFN-γ further activates macrophages and foam cells, and amounts their production of proinflammatory cytokines and chemokines and the process of atherosclerosis is enhanced. This is the second step or wave of inflammatory response activation. The balance between pro- and anti-inflammatory responses regulates the magnitude of the inflammatory response within the plaque, the plaque instability and thrombus formation.

Th1 cells exhibit a strong pro-atherogenic effect that is balanced by anti-atherogenic effect of regulatory T cells and defined cytokines released from Th2 lymphocytes - interleukin- IL-5 and IL-33. Th2 related IL-4 seems to be pro-atherogenic (Chen et al., 2010; Taleb et al, 2010).

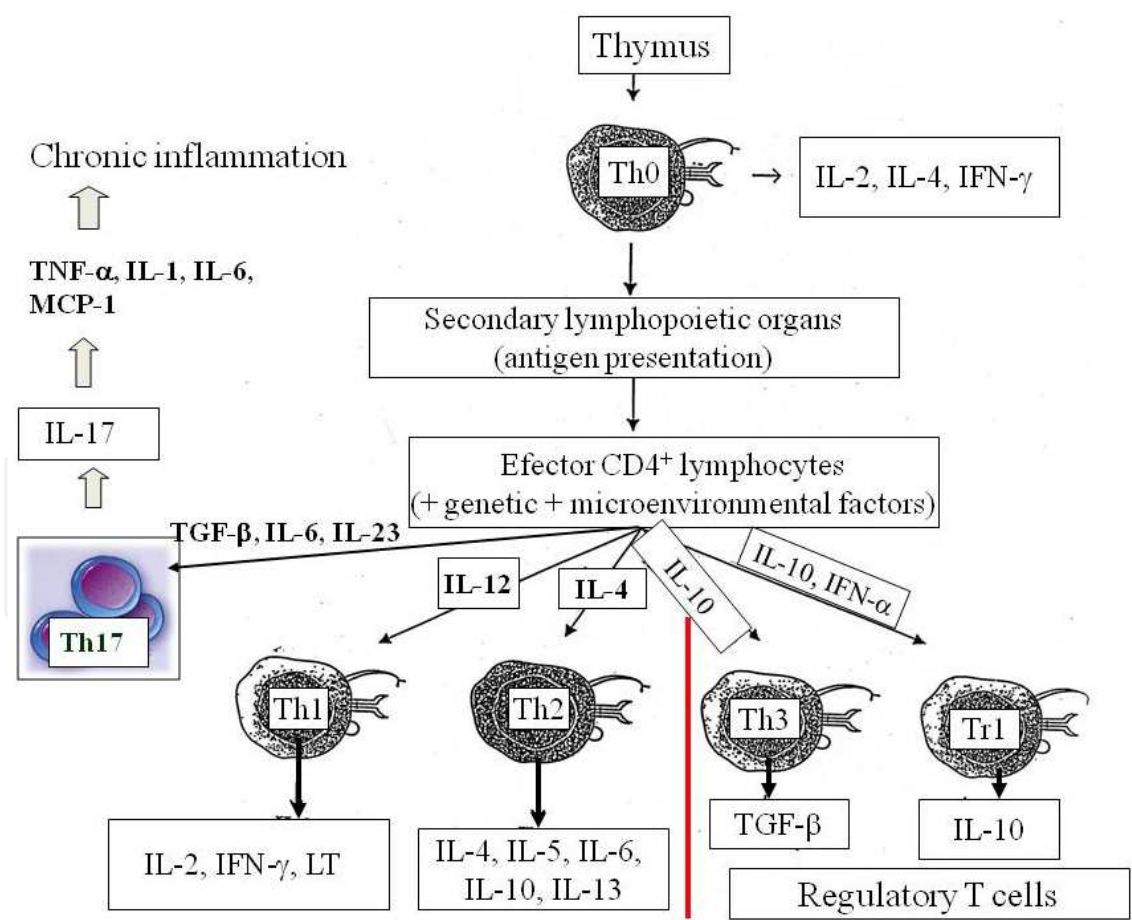


Fig. 2. Th-lymphocytes and cytokines involved in cardiovascular diseases, Polarization of Th-lymphocytes.

Next cells that trigger the inflammatory response in arterial cell wall are Th17 cells, lymphocytes that produce a vast bulk of a strong proinflammatory cytokine IL-17 that leads to elevated production of proinflammatory cytokines TNF- $\alpha$ , IL-1 and IL-6 as well as proinflammatory chemokine MCP-1 (monocyte chemotactic protein) and other neutrophil mobilizing proteins. IL-17 is involved in the pathogenesis of several autoimmune diseases and asthma, its role in atherosclerosis development remains controversial. However, recent studies provide more direct evidence that IL-17 seems to be predominantly pro-atherogenic (Chen et al., 2010).

3. Atherosclerosis and inflammation

Atherosclerosis is an inflammatory disease characterized by vascular injury, lipid accumulation as well as massive infiltration of immune cells in the endothelial wall. Both microbial and self-antigens are responsible for a persistent activation of immune and non-immune cells, thus leading to a condition of chronic smoldering arterial inflammation. At present, atherosclerosis is considered to be an inflammatory disease and atherosclerotic plaque inflammation the cause of intima erosion, rupture and subsequent ischemia (Kraaijeveld et al., 2007; Libby, 2002, Ross, 1999).

Endothelial cell wall inflammation is based on genetic predisposition with mutual interaction between genes and genes, infections and other environmental factors. Repeated inflammatory processes lead to atherosclerosis development, coronary plaque rupture and subsequent ischemia development (Fig. 3).

Endothelial cell wall inflammation - a gradual step-by-step process

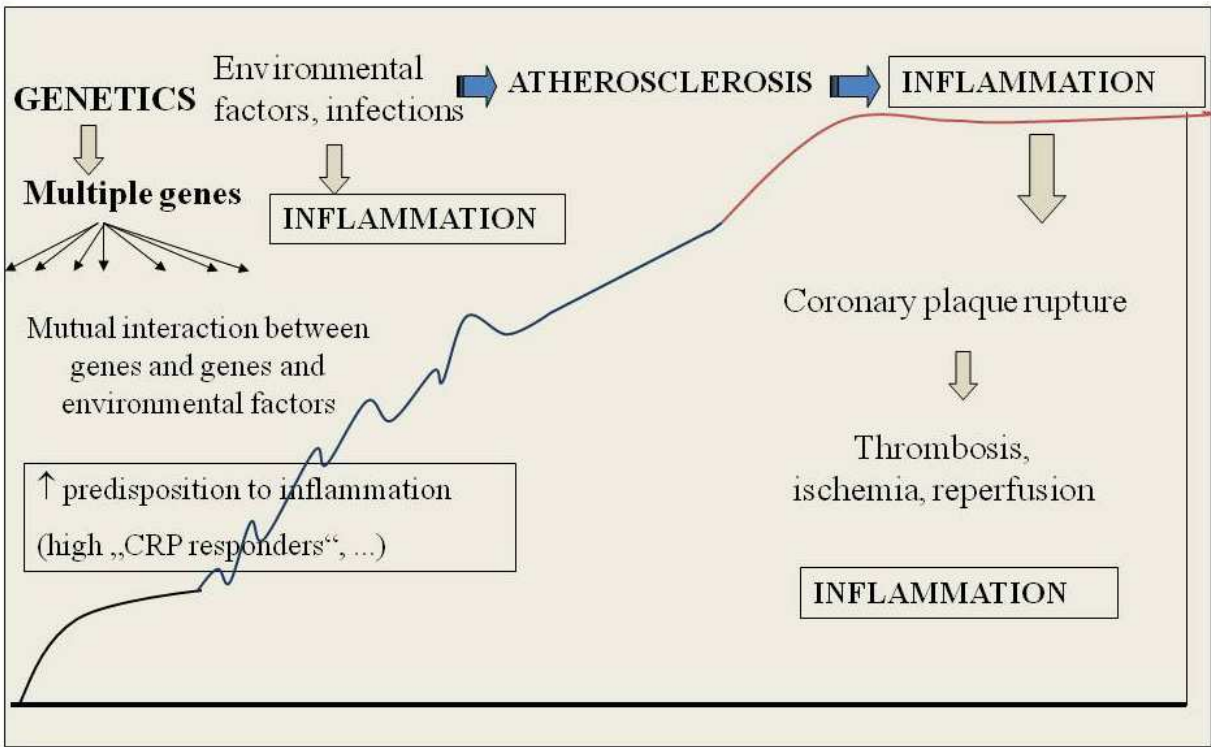


Fig. 3. Inflammation – march to coronary artery disease. A gradual step-by-step process.

The question is, whether the inflammation is the cause or the result of the atherosclerotic plaque rupture. The answer is, both. Intact endothelium is non-sticky and resistant against deposition of any substances into endothelial cell wall (Fig. 4). So, endothelial dysfunction (ED) initiated by both infectious and non-infectious processes (e.g. metabolic syndrome – MetS) is now recognized to play a critical role in the initiation and progression of atherosclerotic vascular disease (Al-Quasi et al., 2008; Bakker et al., 2009; Lamon & Hajjar, 2008). CRP, which levels raise during inflammation contributes to the induction of endothelial cell activation and dysfunction (Deveraj et al., 2010; Grad et al., 2007; Schwartz et al., 2007; Teoh et al., 2008; Venogupal et al., 2003). Patients with MetS have increased plasma levels of oxLDL (Holvoet et al., 2004) and recently it was found that CRP promotes increased oxLDL uptake by vessel wall and cholesterol ester accumulation in Wistar rats (Singh et al., 2008).

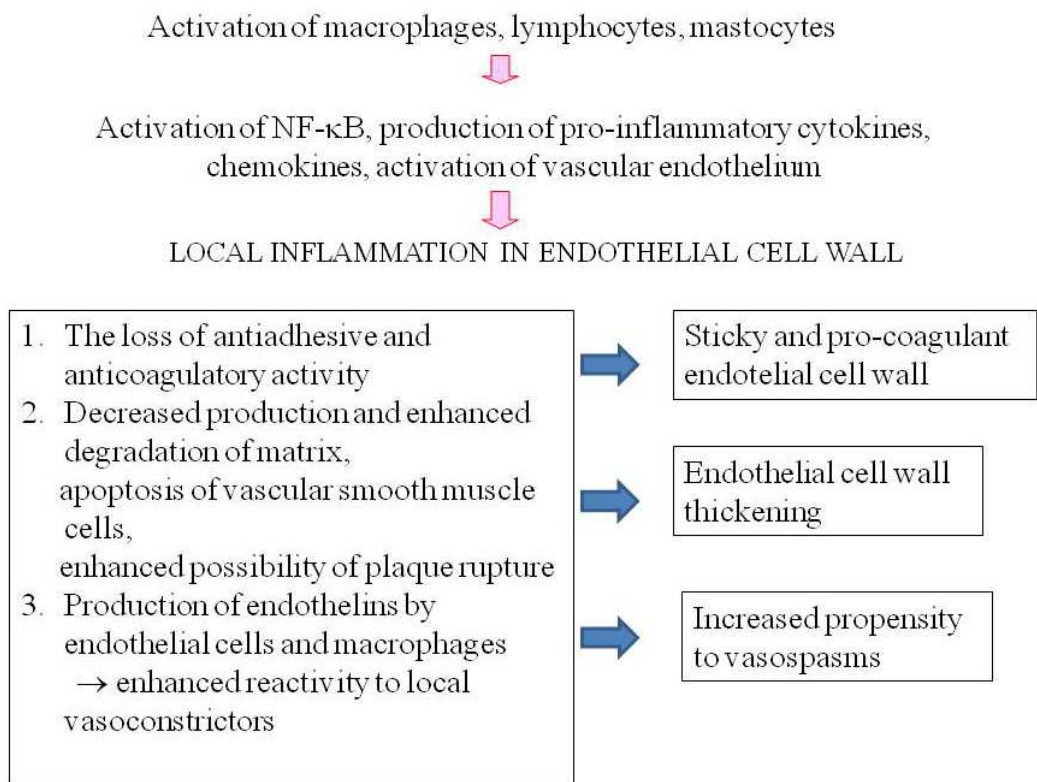


Fig. 4. Local inflammation in endothelial cell wall

Lipid deposition (oxLDL) is accompanied by inflammation – macrophages and T-lymphocytes enter vessel wall and foam cells (macrophages filled with oxLDL particles) develop (Eriksson, 2004). Recruitment of macrophages to the artery wall is one of the first steps in early atherosclerotic lesion formation. Macrophages become activated, produce a large amount of pro-inflammatory cytokines, chemokines and HMGB1 and potentiate inflammation. They release also MMP-9 (matrix metalloproteinase), smooth muscle cells proliferate and intima becomes thickened. Later, fibrosis develops and calcification appears in vessel wall. The more intensive is the inflammation, the higher is the activation of macrophages and atherosclerotic plaque is more unstable, and the thickening of fibrous cap progrediates. In the case of a plaque rupture, tissue factor expressed by activated macrophages facilitate activation of thrombocytes, thrombus formation and subsequent ischemia (Libby, 2002). Critical molecule that is very early released after tissue



ischemia/reperfusion injury is HMGB1 and thereby it functions as early mediator of tissue injury (Chang et al., 2011; Yang et al., 2011).

Chemokines from activated macrophages attract also other immune cells to the site of inflammation – T cells, NK cells and mast cells that aggravate the inflammation. Activated mastocytes support instability of the atherosclerotic plaque by histamine, molecule with pro-inflammatory activity, chymase and tryptase production and support coronary spasm development by the production of endogenous vasoconstrictors. Next mediators are complement components and C-reactive protein (CRP) (Devaraj et al., 2010; Onat et al., 2011). The ability of macrophages to become activated is extremely important in the atherosclerotic plaque rupture. In subjects with a genetically higher ability of macrophage activation, the rupture and subsequent thrombosis and ischemia may develop in a smaller atherosclerotic plaque, even in a limited coronary atheroma (Kondo et al., 2003). This means that two identical atheromas do not need to be identical and differ in their prognosis. The difference is determined by genetic polymorphisms, e.g. by different ability of macrophages to become activated. In particular, the key role of macrophages in this process has been proven by findings in an animal model - mice deficient for macrophage colony stimulating factor were protected from atherosclerosis.

Inflammation of vascular cell wall is a crucial problem and early proinflammatory cytokines, late proinflammatory cytokine HMGB1, chemokines, and acute phase proteins play a great role in it. Key immune system molecules involved in the process of atherosclerosis and cardiovascular disease development are those involved in the process of inflammation and in the process of antigen presentation, monocytes, macrophages, mastocytes and Th1 immunity activation. Preferentially, these are early proinflammatory cytokines TNF- $\alpha$ , IL-1, IL-6, chemokines MCP-1/CCL2, CXCL16, MIP-1- $\alpha$ , proinflammatory cytokine IL-17, late proinflammatory cytokine HMGB1, INF- $\gamma$  - main Th1 macrophage activating cytokine, IP-10 (IFN- $\gamma$  inducing protein) and IL-12, the key Th1 inducing cytokine. On the other hand, IL-10 and TGF- $\beta$  - mediators with anti-inflammatory, immunoregulatory and immunosuppressive activity control this pathology. It was found that besides Th1 lymphocytes, both T cytotoxic cells and NK cells take part in the process of atherosclerosis (Griva et al., 2010; Wang et al., 2010).

In the last years, other molecules as neopterin and procalcitonin are also studied in relation to inflammation and risk of cardiovascular disease development and prognosis. A great interest is devoted to HMGB1.

While acute inflammation serves to resolve pathogen infection and promotes tissue repair, persistent inflammation results in maladaptive tissue remodelling and damage and often serves as the precursor for arterial remodelling that underlies the increase of age-associated arterial diseases. The inflammation plays also an important role in the development of post-ischemic organ dysfunction in acute coronary syndromes, and in the healing process after myocardial infarction (Dewald et al., 2005). These facts highlight the value of non-specific inflammatory markers in patients with cardiovascular diseases.

## **4. Nonspecific inflammatory markers and cardiovascular diseases**

### **4.1 C-reactive protein (CRP). Production, regulation of the production and plasma/serum levels of CRP**

CRP, a part of an acute phase reaction, previously considered to be a marker of underlying infection or tissue injury, was later found also as a marker of chronic low-grade non-

infectious systemic inflammation. Associations between increased levels of CRP and clinical course of the acute MI and other acute coronary syndrome were found (Berk et al., 1990; De Beer et al., 1982; Kardys et al., 2006; Pepys & Hirschfield, 2003).

It was confirmed that CRP is a better risk predictor of the cardiovascular events than LDL levels (Ridker, 2003). Its increased levels are considered a risk factor for atherosclerosis progression and complications even in healthy individuals (Dvorakova & Poledne, 2004). Increased levels of hsCRP were found also in patients with chronic heart failure, diastolic heart failure and dilated cardiomyopathy (Ishikawa et al., 2006; Michowitz et al., 2008; Xue et al., 2006).

At least six major prospective studies support the hypothesis that elevated CRP levels contribute to increased cardiovascular risk (Devaraj et al., 2010; Ridker et al., 2000). These are the Physician's Health Study (PHS) (Ridker et al., 1998), Women's Healthy Study (WHS) (Ridker et al., 2003), Atherosclerosis Risk in Communities (ARIC) study (Ballantyne et al., 2005), and Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) (Downs et al., 1998) in the United States and the Monitoring Trends and Determinants on Cardiovascular Diseases/Cooperative Health Research in the Region of Augsburg (MONICA/KORA Augsburg) (Koenig et al., 2008) and the Age Gene/Environment Susceptibility (AGES)-Reykjavik studies in Europe (Eiriksdottir, 2006).

CRP is nowadays added to so called soluble pattern recognition receptors (PRR), sensors of threatening, that recognize some evolutionary conserved substances both from external intruders on the surface of microorganisms and internal structures that originate from our damaged cells, organs or tissues. Some molecules of danger synthesized during threatening of our organism could also be recognized by CRP (Raz, 2007; Sandor & Buc, 2005). After binding to them, the human CRP activates different humoral factors (the complement system), cells (phagocytes) and transducing signals. That evokes the immune response against the intruders and mediates a potent pro-inflammatory pathophysiological effects, too.

Plasma CRP is produced mostly by hepatocytes and is under the regulation of cytokine IL-6. Normal values range round  $1.3 \text{ mg} \cdot \text{L}^{-1}$  in adults (Maruna 2005). Median CRP levels are somehow higher in apparently healthy adults compared to blood donors and are characteristic for a given individual. CRP levels do not demonstrate seasonal neither diurnal variations and are not influenced by food intake (Pepys & Hirschfield, 2003; Szalai et al., 2002). CRP levels have a tendency to increase with age, reflecting an increased incidence of subclinical pathologic processes (Cеровска et al., 2006; Koenig et al., 1999). After a stimulus, plasma CRP levels increase above  $5 \text{ mg} \cdot \text{L}^{-1}$  in 6 hours, and reach the maximum within 48 hours. After that, the level of CRP returns to very low „reference values“ in plasma with the same speed.

Gene coding for CRP is localized on the chromosome 1 (1q2.1–2.5) and the main inducer of gene transcription is IL-6. IL-1 and complement act synergically (Buc & Bucova, 2007; Cerovska et al., 2006; Krejsek & Kopecky, 2004). The expression of CRP is regulated mainly at transcription level. Post-transcription mechanisms play also an important regulatory role, e.g. during inflammation CRP stay in the endoplasmatic reticulum is shortened from 18 hours to 75 minutes, enabling a faster CRP production (Krejsek & Kopecky, 2004). The half-life of CRP in plasma is approximately 19 hours and is constant during various conditions in healthy and sick people. Therefore, the only factor determining the level of CRP is its production speed (Aukrust et al., 2007), which directly reflects the intensity of pathological process.

4.2 High sensitive CRP (hsCRP)

In the mid of 1990s, a new method ELISA - immunoassay was established to evaluate the level of high sensitive CRP (hsCRP), which has much higher sensitivity than classic methods used previously. It has been proved that higher levels of hsCRP, previously considered to be within normal range, have a strong predictive value in the development of coronary events in the future. First studies concerned patients with stable, unstable and severe unstable angina. These studies showed the predictive value of hsCRP levels regarding future coronary events (Liuzzo et al., 1994; Thompson et al., 1995) and brought a lot of interest into the predictive values of hsCRP. Studies demonstrating the relationship between higher level of hsCRP and future atherothrombotic events, such as coronary events, stroke, peripheral artery disease, were initiated (Arena et al., 2006; Kraus et al., 2007; Ridker et al., 2000). A cardiovascular risk scale according to hsCRP levels was developed (Pearson et al., 2003) (Table 4).

Cardiovascular risk	hsCRP level
Low	< 1 mg . l <sup>-1</sup>
Medium	1 – 2 mg . l <sup>-1</sup>
High	2 – 3 mg . l <sup>-1</sup>
Infection	3 – 10 mg . l <sup>-1</sup>

Table 4. HsCRP scale of cardiovascular risk according to the American Heart Association (Pearson et al., 2003)

4.3 CRP – A contributing factor for increased cardiovascular risk in metabolic syndrome

Metabolic syndrome (MetS) was characterised by a cluster of abnormalities, with insulin resistance and adiposity as central features (Reaven et al., 2005; Eckel et al., 2005; Haffner & Cassells, 2003). Five diagnostic criteria for MetS have been identified by the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III), and the presence of any of these three features – central obesity, dyslipidemia (high triglycerides, low high-density lipoprotein [HDL] cholesterol), hypertension, and impaired fasting glucose – is considered sufficient to diagnose the syndrome (Expert Panel, 2001). About 24% of US adults have MetS, and the prevalence increases with age (44% at age 60 years) (Ford, 2005). 44% of US population over 50 years meeting the NCEP-ATP III criteria has MetS (Alexander et al., 2003).

Metabolic syndrome (MetS) characterised by chronic low-grade inflammation is associated with increased propensity for cardiovascular disease and diabetes development. MetS and cardiovascular disease individuals with MetS have an increased burden of cardiovascular disease (CVD) complications (Devaraj et al., 2010; Lakka et al.; 2002). Men with MetS, even in the absence of baseline coronary artery disease (CAD) or diabetes, had a significantly increased mortality from CAD. It was found that in individuals with MetS, the risk for coronary heart disease (CHD) and stroke was increased threefold (P<0.001) and the risk for

cardiovascular mortality was increased sixfold ( $P < 0.001$ ) (Lakka et al., 2002; Alexander et al., 2003; Devaraj et al., 2004). Individuals with MetS without diabetes had higher CHD prevalence (13.9%), and those with both MetS and diabetes had the highest prevalence of CHD (19.2%) compared with those with neither (Alexander et al., 2003).

Plasma levels of CRP are elevated in individuals with MetS. They were shown to be strongly associated with insulin resistance calculated from the homeostatic model assessment, blood pressure, low HDL, and triglycerides, and also to levels of the proinflammatory cytokines TNF- $\alpha$  and IL-6. Body mass index and insulin resistance were the strongest determinants of the inflammatory state. There is a linear relationship between the number of metabolic features and increasing levels of hsCRP. HsCRP was positively correlated with body mass index, waist circumference, blood pressure, triglycerides, cholesterol, low-density lipoprotein (LDL) cholesterol, plasma glucose, and fasting insulin, and it was inversely correlated with HDL cholesterol and the insulin sensitivity index. The strongest associations were observed between CRP levels, central adiposity, and insulin resistance.

Ridker et al. (2000, 2003) evaluated inter-relationships between CRP, MetS, and incident cardiovascular events among apparently healthy women who were followed for an 8-year period for myocardial infarction, stroke, coronary revascularization, or cardiovascular death. 24% of the cohort had MetS at study entry. They found that women with hsCRP levels of less than 3 mg/L without MetS had the best cardiovascular survival, whereas those with hsCRP levels greater than 3 mg/L with MetS had the worst cardiovascular survival. Other studies also support the hypothesis that an increased hsCRP level in the setting of MetS confers an increased risk of future cardiovascular events.

Thus, it has been proposed that hsCRP should be added as a clinical criterion for MetS and for creation of an hsCRP-modified CHD risk score (Ridker et al., 2000). In addition to the prognostic information that hsCRP evaluation might add to the current definition of MetS, there are several other practical benefits of hsCRP measurement (Devaraj et al., 2010). First, hsCRP is strongly associated with components of MetS that are difficult to measure in routine clinical practice, such as impaired fibrinolysis and insulin resistance (Yudkin et al., 2004, Festa et al., 2000). Also, the widespread availability of commercial assays for hsCRP has made its measurement simple and inexpensive. In addition, as hsCRP does not display diurnal variation and demonstrates long-term stability comparable with cholesterol, it can be reliably evaluated with a single nonfasting measurement. The addition of hsCRP measurement to diagnosis of the MetS may significantly improve the early detection of risk for future diabetes and cardiovascular events in individuals (Ridker et al., 2004).

#### **4.4 CRP, cytokines, chemokines and other nonspecific inflammatory markers**

The level of CRP closely correlates with other non-specific inflammatory markers, which show similar although less significant predictive association with future coronary event (Danesh et al., 1998, 1999). Many studies have shown that increased levels of fibrinogen, CRP and IL-6 are associated with the risk of coronary heart disease, clinical course, prognosis and severity of atherosclerosis (Jenny et al., 2007; Sukhija et al., 2007). Similar association was found with the level of IL-8, where the risk of coronary heart diseases was higher in men compared to women and was independent from both traditional risk factors and CRP (Boekholdt et al., 2004). Authors could not exclude the possibility that IL-8 reflected a pre-clinical atherosclerosis. Concentrations of complement components, mainly the C3 to C4 ratio and the level of BNP (brain natrium uretic peptide) could also predict the



mortality and severity of cardiovascular disease (Blanghy et al., 2007; Iltumur et al., 2005; Palikhe et al., 2007).

Zouridakis et al. (2004) showed 4 markers predicting rapid progression of coronary heart disease – CRP, sICAM (soluble intercellular adhesive molecules), neopterin and MMP-9. Their levels are higher in „progressors“ than in „non-progressors“. According to their results the patients with CRP concentration in the medium quartile had 3-fold risk of coronary heart disease progression compared to the patients in the lowest quartile, and patients with sICAM levels higher than 271,4 ng.ml<sup>-1</sup> (average) had 4-fold increased risk compared to the patients in the lowest quartile. Individuals with neopterin level higher than 7,5 nmol . L<sup>-1</sup> (medium quartile) have 5-fold increased risk of coronary heart disease development and progression compared to individuals with neopterin levels in the lowest quartile. Patients with MMP-9 concentration higher than 47,9 µg.l<sup>-1</sup> (median) have 3-fold increased risk of coronary heart disease progression compared to the patients in the lowest quartile. As the last two markers are indicators of the activity of macrophages that are key cells playing a causative role in the process of atherosclerosis, the evaluation of their activity seems to be useful in patients at risk. A systemic therapy might prevent development or progression of coronary heart disease.

#### **4.5 CRP and proinflammatory cytokines – The cause and the result of the inflammatory process**

It is questionable to what extent are pro-inflammatory cytokines and CRP purely acute phase markers and to what extent are they active inflammatory participants. Increased levels of IL-6 were found in patients with unstable angina, where inflammatory reaction may promote conversion of a stable atherosclerotic plaque to an unstable one (Biasucci et al., 1996). It was also found that plasma CRP level can predict future cardiovascular events or mortality due to coronary heart disease even in healthy individuals (Dvorakova & Poledne, 2004; Kardys et al., 2006; Koenig et al., 2006). CRP predicts cardiovascular risk even in Japanese, who generally have lower levels (Saito et al., 2007). These findings show the possibility that both the progression of atheroma and the plaque rupture might be predicted by a follow-up of CRP levels. The role of TNF-alfa and IL-6 in the atherogenesis and thrombosis was also shown. Pro-inflammatory cytokines TNF-alfa, IL-6, IL-1 and also CRP are in large amounts produced except of liver also by adipocytes (Mohamed et al., 1997; Yudkin et al., 1999). Production of IL-6 in obese patients and approximately 30% of IL-6 in healthy individuals comes from adipocytes. These cytokines inhibit insulin signalization and cause insulin resistance, and also enhance the development of endothelial dysfunction – they increase the expression of adhesive molecules, pro-thrombotic factors, acute phase proteins, which can increase a cardiovascular risk via a feed back mechanism (Conen et al., 2006; Kremen et al., 2006). It was found that, both CRP and pro-inflammatory cytokine levels correlate with blood pressure, dyslipidemia, HDL (high density lipoprotein cholesterol) and level of triglycerides, smoking, diabetes, insulin resistance, markers of endothelial dysfunction and obesity (Bermudez et al., 2002; Cerovska et al., 2006; Chambers et al., 2001; Dvorakova & Poledne, 2004; Ford, 1999; Frohlich et al., 2000). The correlation with BMI (body mass index) was also found, which could partially reflect the fact that the majority of basal CRP and IL-6 is produced in adipocytes (Danesh et al., 1999). Weight decrease was associated with plasma CRP decrease even in healthy individuals (Mohamed-Ali et al., 1997).



In the pathogenesis of coronary heart disease and atherosclerosis, chemokines play an important role, too. The most important are: MCP-1 (monocyte chemotactic protein), MIP-1 $\alpha$  (macrophage inflammatory protein), IP-10 (IFN-gama inducible protein, with  $M_r = 10\,000$ ), RANTES (regulated on activation normal T-cell expressed and secreted) and eotaxin (Rothenbacher et al., 2006). MCP-1, called also CCL2 (MCP-1/CCL2) is chemotactic to monocytes, T-lymphocytes and NK cells and participates in the development and restoration of diseases characterized with infiltration of monocytes (Gu et al., 1998; 1999). It modulates fibroblasts and endothelial cells function and has an important role in the pathogenesis of myocardial infarction, thrombotic occlusion, myocardial ischemia, and also in the reperfusion and healing process after myocardial infarction (Dewald et al., 2005). Tarzami et al. showed that MCP-1/CCL2 had a dual role in myocardial ischemia – beside chemotactic activity protected myocardial cells against hypoxia induced cell death (Tarzami et al., 2002; 2005).

#### **4.6 Non-specific inflammatory markers in cardiovascular diseases – what do they reflect?**

Another question is, what exactly these non-specific markers reflect. Four possibilities can be found and three of them directly or indirectly highlight the role of atherosclerosis: 1. Atherosclerosis, plaque development, its instability, rupture and resulting atherothrombosis are inflammatory events. The first assumption could be that increased levels of inflammatory markers reflects inflammation of the vessel wall. This is possible, but some contradictory results concerning the level of CRP and atherosclerotic plaque size exist. This discrepancy could be explained by genetic polymorphism causing a different ability of macrophages to be activated as it was mentioned above, which explains a possible rupture even in a small atherosclerotic plaque (Kondo et al., 2003). Chronic systemic non-vascular infection is also pro-atherogenic and acute systemic inflammatory episodes are markedly associated with atherosclerotic processes (Rothenbacher et al., 2006). CRP could reflect inflammation in some other part of organism, although the correlation of Chlamydia pneumoniae and Helicobacter pylori antibodies with the development of coronary heart disease is not very clear (Danesh et al., 2000). Generally, the above mentioned associations of CRP and IL-6 levels with BMI and IHD risk factors increase the possibility that inflammatory markers associated with the risk of atherothrombosis could reflect a certain metabolic state, which is also pro-atherogenic and is a predisposition to atherothrombotic events, that means it is also pro-inflammatory. In fact, CRP level predicts development of type 2 diabetes independently from traditional risk factors (Freeman et al., 2002). In insulin-resistant obese individuals, increased CRP levels decrease in parallel with the improvement of insulin resistance related to weight loss (Mc Laughlin et al., 2002). The fourth possibility is the fact that individuals differ in their sensitivity to various stimuli leading to acute phase proteins production. Therefore, those who are „higher CRP responders“, either due to genetic mechanism or other acquired mechanism (for example, BMI) are simple more sensible to atherosclerosis progression and complications.

#### **4.7 CRP - a cause of cardiovascular disease**

CRP has been traditionally thought to be a bystander marker of vascular inflammation, without playing a direct role in CVD. Now, increasing evidence suggests that CRP may directly contribute to the proinflammatory state, and play thus a direct role in vascular injury.

Aggregated CRP binds to and opsonizes LDL and VLDL (very low density lipoprotein), subsequently activates complement and mediates uptake of these particles by macrophages that transform into foam cells (Pickering et al., 2007; Thomson et al., 1995).

Several reports demonstrated the presence of CRP within atheromatous plaque where it precedes and mediates monocyte recruitment (Jian-Jun & Chun-Hong, 2004). CRP was found to be widely distributed in early human atherosclerotic lesions of human coronary arteries with two predominant manifestations. First, the majority of foam cells below the endothelium showed positive staining for CRP. This staining was clearly cell associated, mainly along the cell surface. Second, CRP was deposited diffusely rather than focally in the deep fibroelastic layer and the fibromuscular layer of the intima adjacent to the media (Cеровска et al., 2006). CRP activates the classical pathway of complement and has been shown to colocalize with the membrane attack complex (C5b-C9) in early atherosclerotic lesions in the fibromuscular layer of the intima, which contains predominantly smooth muscle cells (Cеровска et al., 2006; Szalai et al., 2002).

CRP can stimulate tissue factor production by macrophages, the main stimulus for initiating coagulation, upregulates the expression of adhesion molecules ICAM-1 and VCAM-1 (vascular adhesion molecule-1) by endothelial cells and mediates proinflammatory factor induction in artery wall as well as circulating monocytes (Aukrust et al., 2007; Liuzzo et al., 1994; Kraus et al., 2007; Pickering et al., 2007). In addition, CRP mediates MCP-1 induction in endothelial cells (Aukrust et al., 2007; Liuzzo et al., 1994).

CRP also stimulates the release of inflammatory cytokines TNF- $\alpha$ , IL-1 $\beta$ , IL-6 and may also directly act as a proinflammatory stimulus to phagocytic cells by binding to the FcRII receptor (Buc & Bucova., 2007). Furthermore, monocytes from healthy subjects were also found to exhibit an enhanced production of IL-6 in response to CRP and this response was significantly inhibited by simvastatin in a dose-dependent manner (Krejsek & Kopecky., 2004). IL-6 production increases very rapidly, 4 h after CRP stimulation and therefore continues to rise at a slower rate, reaching a peak at 24 h.

Devaraj et al. (2009) outlined that CRP contributes to increased cardiovascular risk by inducing endothelial cell dysfunction and activating monocytes.

These data suggest that CRP may indeed be a direct proinflammatory factor involved in the initiation and progression of atherosclerosis.

#### 4.8 HMGB1

HMGB1, formerly known as a nuclear nonhistone protein, that stabilizes nucleosomes, has DNA-binding properties, facilitates gene transcription, and has an essential position in DNA repair (Lange & Vasquez, 2009; Lotze & Tracey, 2005; Wang et al., 2007.). Later studies identified the extracellular form of HMGB1 as a critical mediator of inflammation, mainly sepsis and also as a factor that promotes tissue repair and regeneration (Fink, 2007; De MR et al., 2007; Klune et al., 2008).

HMGB1 is likely to be released into extracellular milieu in two ways - passively from necrotic or injured cells (e.g. after ischemic/reperfusion injury - IRI) and actively by activated monocytes and macrophages (Ulloa & Messmer, 2006). This extracellular HMGB1 acts as alarmin and signaling through RAGE, TLR2 and TLR4 leads to the activation of NF- $\kappa$ B, which induces the production of proinflammatory cytokines and angiogenic factors in both hematopoietic and endothelial cells.

Its key role has been revealed in lethal endotoxemia and sepsis and as it is released later than other pro-inflammatory cytokines (after 16-32 h) it became known as a "late mediator

of sepsis” or “late proinflammatory cytokine” (Wang et al., 1999, 2007). Recently identified biological activities of HMGB1 include chemotactic activity, activation of monocytes/macrophages to release proinflammatory cytokines, upregulation of endothelial cell adhesion molecules, stimulation of epithelial cell barrier failure, and mediation of fever and anorexia (Wang et al., 2004). More recently, HMGB1 was recognized as a proangiogenic factor, and seems to be able to attract also stem cells to the area of injury and inflammation, activate them and promote thus healing and regeneration (De MR et al., 2007; Klune et al., 2008). Interestingly, HMGB1 can act also on local stem cells, activate them, promote their differentiation and facilitate the healing process directly from local sources (Lolmede et al., 2009; Yiang et al., 2010). The discovery of HMGB1 as a critical mediator of inflammation in different inflammatory diseases has stimulated tremendous interest in the field of inflammation research. HMGB1 protein contributes to development of autoimmune diseases, and its role in growth and spread of many types of tumours has also been revealed (Abdulahad et al., 2010; Tang et al., 2010). Thus, HMGB1 represents a potential target in therapy of various disorders related to inflammation (Yang and Tracey, 2010).

HMGB1 is structurally composed of three different domains: two homologous DNA-binding sequences entitled box A and box B and a highly, negatively charged C terminus. The B box domain is responsible for proinflammatory activity of the molecule, whereas the A box region has an antagonistic, anti-inflammatory effect with therapeutic potential. Administration of highly purified, recombinant A box protein or neutralizing antibodies against HMGB1 rescued mice from lethal sepsis (Huang et al., 2010).

Many recent studies demonstrated that HMGB1 played a pivotal role in cardiovascular diseases, such as atherosclerosis, myocardial ischemia/reperfusion injury (IRI), heart failure, and myocardial infarction. Elevated levels of HMGB1 has been detected in patients with coronary artery diseases (CAD), in patients with cerebral and myocardial ischemia, in IRI of the heart and is a novel predictor of adverse clinical outcomes after acute myocardial infarction (Goldstein et al., 2006; Kohno et al., 2009; Yan et al., 2009).

Injury of endothelium is essential for the initiation of atherosclerosis as it leads to the attraction of macrophages. Progression of atherosclerosis goes along with prolonged pro-inflammatory response (Mullaly and Kubes 2004). It was revealed that HMGB1 and RAGE are expressed in endothelial cells, smooth muscle cells, and macrophages of atherosclerotic lesions (Kalinina et al., 2004). Moreover, activated vascular smooth muscle cells are the source of HMGB1 in human advanced atherosclerotic lesions (Innoue et al., 2007). Therefore, up-regulation and secretion of HMGB1 may lead to intensification of inflammatory response in endothelial lesions, promote further atherosclerotic changes and thus may be related to the severity of coronary artery stenosis (Innoue et al., 2007).

#### **4.8.1 HMGB1 in ischemic and reperfusion injury**

Many factors have been revealed to be involved in IRI including nitric oxide or plenty of cytokines released under proinflammatory conditions in the afflicted area in many organs i.e. heart, brain, kidney or liver (Matsuki et al., 2006; Hsieh et al., 2007). Recent studies suggest potential implication of HMGB1 in the pathogenesis of IRI (Goldstein et al., 2006). IRI leads to tissue damage and high amounts of HMGB1 protein are released around the central ischemic area (Kim et al., 2006).

#### **4.8.2 HMGB1 in positive feedback mechanism**

HMGB1 seems to be involved in positive feedback mechanism, that may help to sustain inflammation and angiogenesis and contribute thus to disease progression. CRP dose

independently induces the production of HMGB1 through the p38 MAPK pathway (Kawahara et al., 2008). In return, HMGB1 triggers the expression of other proinflammatory cytokines and reinforces this way the proinflammatory process (Andersson et al., 2000; Wang et al., 1999). Endothelial cells express HMGB1, as well as its receptors RAGE, TLR2 and TLR4 and signalling through these receptors leads to activation of NF $\kappa$ B, which can subsequently induce the expression of HMGB1 receptors (van Beijnum et al., 2008). These studies suggest that HMGB1 may be a critical proinflammatory cytokine and may play an important role in the pathogenesis of CAD.

Hu et al. (2009) has found markedly increased level of serum HMGB1 that correlated with severity of coronary artery stenosis in patients with stable (SAP) and unstable angina pectoris (USAP), especially in SAP patients. In addition, a strong correlation between angiographic Gensini score and serum level of HMGB1 has been found. However, in subgroup analysis the serum level of HMGB1 was significantly correlated only with angiographic Gensini score in SAP patients, not USAP patients. These results indicated, that the level of serum HMGB1 may predict the degree of coronary artery stenosis in patients with SAP and HMGB1 may be involved in the pathogenesis of USAP (Hu et al., 2009). The serum level of HMGB1 positively correlated with the serum level of hs-CRP, TNF- $\alpha$  and IL-6 in patients with CAD (Hu et al., 2009; Yan et al., 2009). These results are in agreement with previous observations that there is a cross-talk between HMGB1 and other proinflammatory cytokines and CRP.

Passively released from necrotic cells or actively secreted by activated monocytes/macrophages, or other cells, HMGB1 functions as an inflammatory stimulus that upregulates the production of early proinflammatory cytokines TNF- $\alpha$ , IL-1, IL-6, and different inflammatory proteins (MIP-1 $\alpha$ , MIP-1 $\beta$ ), and subsequently CRP (Andersson et al., 2000; Sama et al., 2004). Interestingly, HMGB1 alone can directly stimulate the production of CRP which is an independent predictor of coronary artery disease extent in patient with stable and unstable angina pectoris (Arroyo-Espliguero et al., 2009; Niccoli et al., 2008).

#### 4.8.3 HMGB1 and therapy in cardiovascular diseases

HMGB1 is considered as a potential clinical therapy, in association with myocardial infarction. The possibility of evaluating HMGB1 as a regenerative and proliferative agent in the myocardium was first suggested by Palumbo et al. (2004). They demonstrated that HMGB1 induced migration and proliferation of blood vessel mesangioblasts, which are blood vessel stem cells. Later, Limana et al. (2005) discusses the role of HMGB1 in initiating activation and differentiation of endogenous cardiac stem cells in a mouse model of myocardial infarction. The capacity of HMGB1 to promote the development of mouse cardiomyocytes and initiate repair of myocardial infarction is quite remarkable. An exogenous HMGB1 directly injected to peri-infarcted area contributes to increased amount of myocytes inside the area of infarcted cardiomyocytes that goes along with improved outcome confirmed by structural and functional measures (Klune et al., 2008; Limana et al., 2005). These examples support effect of HMGB1 in regenerative processes.

Human cardiac stem cells (CSCs) can be obtained fairly readily from cardiac surgery specimens, and they have been characterized to a very limited extent. As such, it is too early to comment on similarities and differences between mouse and human CSCs, as too little is known about adult human CSCs. Moreover, the use of HMGB1 like any other drugs or molecules that activate resident stem cells in vivo might circumvent the need for „classical“ stem cell therapy. Interestingly, the mechanism by which HMGB1 works is not yet clear.



They current working hypothesis is that it functions by interfering with pro-apoptotic pathways (Rosenberg & Oppenheim, 2007).

#### 4.9 Neopterin

Among the immune inflammatory cells, activated macrophages contribute significantly to atherosclerosis plaque progression, fibrous cap disruption and intracoronary thrombus formation (Avanzas & Kaski, 2009). Macrophages are a marker of unstable atherosclerotic plaque, may release lytic enzymes that degrade the fibrous cap, produce rupture of the atherosclerotic plaque and therefore play a significant role in the pathophysiology of acute coronary syndrome (Moreno et al, 1994).

IFN-gama - a cytokine produced by activated Th1 cells is centrally involved in atherosclerosis - related inflammation and monocyte/macrophage activation and contributes to this process. In activated macrophages IFN-gama stimulates conversion of tryptophan to kynurenine and production of neopterin (Pedersen et al., 2011). Enhanced tryptophan degradation in patients with coronary heart disease was found to correlate with enhanced neopterin formation.

Neopterin, a pteridine, by-product of the guanosine triphosphate pathway is an activation marker for monocytes/macrophages (Sugioka et al., 2010a, 2010b), marker of inflammation and Th1 immune system activation (Pacileo et al., 2007; Murr et al., 2002). In the past several years, the measurements of neopterin concentrations in body fluids including plasma, serum, urine and cerebrospinal fluid has revealed its potential role in the prediction of long-term prognosis in both patients with viral infections, HIV-1 infection, severe systemic inflammatory diseases, several autoimmune diseases, renal transplant rejection, cancer (Kozłowska-Murawska & Obuchowicz, 2008; Plata-Nazar et al., 2004; Sucher et al., 2010). By neopterin measurements, not only the extent of monocyte/macrophage and Th1 immune system activation but also the extent of oxidative stress could be estimated (Murr et al., 2002).

Elevated plasma/serum levels of neopterin have also been reported in patients with coronary disease compared to controls and in recent years it has become apparent that increased neopterin concentrations are an independent marker for cardiovascular disease (Fuchs et al., 2009). Neopterin serves also as a good biomarker of plaque inflammation, its instability in both coronary and carotid atherosclerotic lesions (Sugioka et al., 2010a), and as a marker for cardiovascular risk (Avanzas & Kaski, 2009). In particular, neopterin predicts future major cardiac and vascular adverse events in patients suffering from coronary artery disease (Avanzas et al., 2005; De Rosa et al., 2011; Pacileo et al., 2007). Serum neopterin is an independent predictor of major adverse coronary events and may also serve as a useful marker for risk stratification in patients with chronic stable angina pectoris.

Coronary angiographic studies have shown a relationship between increased circulating levels of neopterin and the presence of complex coronary lesions in patients with unstable angina pectoris. Moreover, higher prevalence of neopterin-positive macrophages was found in culprit lesions in patients with UAP than in those with stable angina pectoris (SAP), so neopterin could serve as an important biomarker of plaque instability in both coronary and carotid atherosclerotic lesions (Sugioka et al., 2010a, 2010b). However, plasma neopterin levels were significantly higher also in SAP patients with complex carotid plaques than those in noncomplex plaques (Sugioka et al., 2010b). This marker of macrophage activation may be useful for risk stratification even in patients with chronic stable angina (Avanzas et al., 2005).



Left ventricular ejection fraction (LVEF) is the strongest predictor of survival in patients with chronic stable angina (CSA). Baseline neopterin levels - but not CRP - showed a significant inverse correlation with LVEF. Increased serum neopterin concentrations inversely correlate with LVEF values and high neopterin levels are a predictor of LV dysfunction in patients with CSA, irrespective of the extent and severity of coronary artery disease. Neopterin may thus be clinically useful for patient risk stratification (Estévez-Loureiro et al., 2009).

#### 4.10 Procalcitonin

Procalcitonin (PCT) was originally described in 1984 as a 116 amino-acid protein and now is known as a highly selective and specific marker for early diagnosis of sepsis. Procalcitonin (PCT) - prohormon of calcitonin, is under basal condition produced only by C-type cells of thyroid and neuroendocrine cells of the lung. Thus, the basal plasma level of PCT in healthy individuals is very low, under detection limit - below 0.05 ng/ml. Under systemic bacterial infection preferentially of bacterial origin, the levels of PCT raise very quickly because almost all cells of human body start to be the source of PCT and the level of this molecule rapidly increases, it can reach several hundred of ng/ml. That is why is PCT considered as a hormokine, an acute phase marker and an early marker of systemic bacterial infection. The levels of PCT are elevated also under the conditions of non-infectious systemic inflammatory processes, this elevation is not so high. Elevation of PCT is mediated directly by microorganisms or indirectly by pro-inflammatory cytokines (Bucova, 2005).

So far, data on plasma/serum PCT levels in patients with cardiogenic shock and in those with acute coronary syndromes (ACS) are scarce and controversial. While some studies report that PCT levels are increased in ACS patients on admission, other investigations document that plasma PCT concentrations are in the normal range. Ataoğlu et al. (2010) found that higher PCT levels within 48 h post-admission may reflect an inflammatory state that is associated with increased early and 6-month mortality. Picariello et al. (2009) reported that the degree of myocardial ischemia (clinically indicated by the whole spectrum of ACS, from unstable angina to cardiogenic shock following ST-elevation myocardial infarction) and the related inflammatory response are better reflected by C-reactive protein than by PCT, which seems to be more sensitive to a higher degree of inflammatory activation, being positive only in patients with cardiogenic shock. Few studies investigated the dynamics of PCT in cardiac acute patients, and, despite the paucity of data and differences in patients' selection criteria, an increase in PCT values seems to be associated with the development of complications. In acute cardiac patients, the clinical values of procalcitonin rely not on its absolute value, but only on its kinetics over time (Picariello et al., 2009).

## 5. Genetic background of inflammation in cardiovascular diseases

### 5.1 Main terms

People differ in the risk of development and death due to various diseases including cardiovascular disease, and differ also in inflammatory reactions (Bucova et al., 2008a; Javor et al., 2007). Inter-individual genetic differences play an important role.

Human diseases are roughly divided into three categories according to genetic factors: 1. „monogenic diseases“ (caused by one gene defect), 2. complex diseases (with multigenic or polygenic predisposition) and 3. diseases without genetic predisposition. The best results were achieved in „monogenic diseases“. Recently, the attention is shifted to complex diseases caused by several genes, including majority of socially burden diseases (Fig. 5).

### Single nucleotide polymorphism - SNP:

...AGCAGGATTAGATTACTTTAA... – *allele 1*  
 ...AGCAGGAGTAGATTACTTTAA... – *allele 2*

### Repetition polymorphisms:

...GATAGTCTCCTAGTGCGTAC... – *allele 1*  
 ...GATAGTCTCCTCTAGTGCGTAC... – *allele 2*  
 ...GATAGTCTCCTCTCTAGTGCGTAC... – *allele 3*

Fig. 5. The most frequent DNA polymorphisms

Genetic polymorphism means that more than one allele (variant) of gene is present in population. It is referred to when the frequency of the most frequent gene allele in population is lower than 99%, e.g. when the frequency of the rare gene allele is higher than 1%. Single nucleotide polymorphism (SNP) belongs to the most common types of genetic polymorphism, including exchange, insertion or deletion, and repetitive polymorphisms (Fig. 5). The number of SNP polymorphisms in genome is estimated to 10 millions (Hafler et al., 2005). Gene variants, influencing gene expression, are called functional gene polymorphisms. SNP polymorphism may be present in coding, regulatory and in non-coding gene regions (Tsuchiya et al., 2002).

While the polymorphisms in coding regions tend to change the structure of primary protein or result in protein defect, the polymorphisms in regulatory gene areas, influencing gene transcription, may affect gene expression. It is suggested that majority of polymorphisms playing a role in genetic predisposition of complex diseases, are found in regulatory gene areas (Tsuchiya et al., 2002).

Individual genetic susceptibility to complex diseases is present, when an inter-individual difference in disease risk exists, not determined by environmental factors. Regarding diseases, we distinguish susceptibility gene variants (allele), which predispose for disease development (they are more frequently found in patients compared to general population) and protective alleles, which on the contrary, are less common in patients than in healthy subjects.

## 5.2 Genetics, inflammation and cardiovascular diseases

The inheritance of cardiovascular diseases is polygenic, i.e. several genes can influence their development and clinical course. Except of polymorphisms of genes coding for homocystein, lipid metabolism, factors of coagulation,  $\beta_2$  – adrenergic receptors, genes regulating blood pressure and others, inflammatory factors genes play an important role, too (Arnett et al., 2007; Horne et al., 2007; Markovic et al., 2007; Ozanne et al., 2007). These genes are numerous and gene polymorphisms related to different stages of inflammatory response have been found (Andreotti et al., 2002; Bernardo et al., 2006; Espliguero et al., 2005).

### 5.2.1 Genetics of CRP

The basal level of CRP both in patients and healthy controls are genetically determined. In repetitive measurements in healthy individuals it was found that concentrations of CRP

were relatively stable. It means, that knowledge in CRP genetic component may contribute to the stratification of so far healthy individuals into groups with higher or lower risk for cardiovascular disease development (Crawford et al., 2006; Szalai et al., 2005).

The human CRP gene lies on chromosome 1, within a conserved region that encodes for proteins critical to the immune system and to intercellular communication (Bucova et al., 2008b; D'Aiuto et al., 2005, Suk et al., 2005). Dupuis et al. (2005) found that multiple genes on chromosome 1 may influence inflammatory biomarker levels and may have a potential role in development of cardiovascular disease. They hypothesised that production of biomarkers of vascular inflammation is modulated both genetically and by environmental factors.

Family studies estimates of CRP ranging from 27–40%, and it is hypothesized that genetic variation in the CRP gene may influence plasma CRP levels and subsequent risk of CHD. Several studies have reported individual single nucleotide polymorphisms (SNPs) to be associated with CRP levels and Risk of Incident Coronary Heart Disease in Two Nested Case-Control Studies.

Szalai et al. (2005) sequenced 1156 nucleotides long promoter area of the CRP gene and identified two SNPs - one bi-allelic (-409A/G) and one three-allelic (-390C/T/A), which modulated basal CRP concentration in healthy individuals by influencing transcription factor binding. The results of „Framingham heart study“ in 1640 unrelated participants revealed in 9 from 13 studied SNPs a relationship with CRP level (Kathiresan et al., 2006). Knowing factors, which regulate plasma CRP levels, either basal or induced by infection or other inflammation, is very important also for the cardiovascular risk prediction. It was found that patients with homozygous +1444TT allele of CRP gene had significantly higher plasma CRP levels induced by inflammatory stimulus (D'Aiuto et al., 2005). This effect was independent from IL-6 concentration, IL-6 -174G/C SNP and conventional cardiovascular risk factors.

The production of CRP is except of CRP gene regulated also by other genes coding for IL-6, IL-1 beta and IL-1Ra (Fishman et al., 1998; Kathiresan et al., 2006; Latkovskis et al., 2004; Szalai et al., 2005; Vickers et al., 2002). In 160 patients with angiographically confirmed coronary heart disease, the association of higher plasma CRP level with the presence of IL-1B (+3954)T allele was found as well as a possible relationship between IL-1RN(VNTR)\*2 allele and lower CRP concentrations (Latkovskis et al., 2004).

Acute coronary syndrome is associated with the activation of endothelial cells and systemic inflammation. It was found that genetic variations in the IL-1 locus influenced inflammatory processes - the IL-1RN\*2 and the -511 alleles, respectively, contributed to changes in the plasma level of soluble markers of endothelial inflammation such as von Willebrand factor (vWF) and E-selectin (Ray et al., 2002). A correlation between higher plasma CRP level and presence of CD14 260TT homozygous allele was also found, which could be associated with the higher ability of macrophages to become activated and produce pro-inflammatory cytokines (Bernardo et al., 2006; Espliguero et al., 2005).

Bucova et al. (2009a) found an association of MCP-1 -2518 A/G single nucleotide polymorphism with the serum level of CRP in Slovak patients with ischemic heart disease, angina pectoris, and hypertension.

Additionally, a genome-wide association study has been performed among 6 345 apparently healthy women in whom 336 108 single nucleotide proteins were evaluated as potential determinants of plasma CRP concentration (Devaraj, 2010). Overall, seven loci that associate with plasma CRP levels were found. It was concluded that common variations in several genes involved in metabolic and inflammatory regulation have significant effects on CRP

levels, consistent with the identification of CRP as a useful biomarker of risk for incident vascular disease and diabetes. Two of these loci (GCKR and HNF1A) are suspected or known to be associated with maturity-onset diabetes of the young, one is a gene-desert region on 12q23.2, and the remaining four loci are in or near the leptin receptor protein gene, the apolipoprotein E gene, the IL-6 receptor protein gene, or the CRP gene itself. The protein products of six of these seven loci are directly involved in MetS, insulin resistance,  $\beta$ -cell function, weight homeostasis, and/or premature atherothrombosis.

Thus, there is a possibility that individuals vary in their sensitivity to intercurrent low-grade acute-phase stimuli to which everybody is exposed, and that those who are higher “CRP responders” through genetic and/or acquired mechanisms, are also more susceptible to progression and complications of atherosclerosis (Dewald et al., 2005).

Understanding the factors that directly or indirectly regulate the CRP release at baseline and during inflammation is very important in context of coronary risk prediction. More scientific groups studied CRP gene polymorphisms and found that basal levels of CRP both in patients and healthy controls are genetically determined and under repeated examination in healthy subjects relatively stable. Thus understanding the genetic background of CRP that regulate basal but also by infection or any type of inflammation induced concentration of CRP might contribute to stratification of healthy subjects to different groups with higher or lower degree of cardiovascular disease development (Cermakova et al., 2005; Pearson et al., 2003; Szalai et al., 2002)

### **5.2.2 Gene polymorphisms of MCP-1/CCL2 and CCR2 and the risk of cardiovascular disease development**

Pro-inflammatory cytokines and chemokines play an important role in the pathogenesis of heart diseases (Rothenbacher et al., 2006). Gene polymorphisms of chemokine MCP-1/CCL2, a molecule that plays an important role in atherosclerosis, and its receptor CCR2 belong to most studied one (Arakelyan et al., 2005; Bucova et al., 2008a; Petrakova et al., 2003). MCP-1/CCL2 is a potent chemoattractant for monocytes, T cells and NK cells. MCP-1 induces the transmigration of CCR2<sup>+</sup> monocytes from the circulation, promotes their differentiation to lipid-laden macrophages (Gerszten et al., 1999; Tabata et al., 2003) and contributes to the proliferation of arterial smooth muscle cells (Viedt et al., 2002) which, along the macrophages, constitute the key cellular components of atherosclerotic plaques. This chemokine plays a dual role in myocardial ischaemia. In addition to several negative roles in the process of atherosclerosis, thrombotic occlusion of a coronary artery and in the process of reperfusion, this chemokine protects myocytes from hypoxia-induced cell death and has also positive effect in myocardial infarct healing (Dewald et al., 2005; Tarzami et al., 2002, 2005).

Polymorphism of MCP-1 and its receptor CCR2 have been implicated as susceptibility factor for chronic stable angina pectoris, ischemic heart disease and myocardial infarction by several independent investigators (Petrakova et al., 2003; Ortlepp et al., 2003), even in hypertensive ischemic heart disease asymptomatic patients (Penz et al., 2010). An association of CCR2 polymorphisms with the number of closed coronary artery vessels in coronary artery disease was also found (Cha SH et al., 2007). Deletion of MCP-1/CCL2 or CCR2 resulted in a large (50%-80%) reduction in atherosclerotic plaque size (Boring et al., 1998; Gu et al., 1999). However, the data on contribution of the MCP-1 polymorphisms to the pathogenesis of coronary atherosclerosis are not uniform. McDermott et al. found that the presence of MCP-1 -2578G allele in homozygous form was significantly associated with



both myocardial infarction occurrence and higher MCP-1 plasma level. Increased MCP-1 levels were associated with age, smoking, BMI and waist to hip ratio (Mc Dermott et al., 2005). In other study, the plasma MCP-1 level was independently associated with the prognosis of patients with acute coronary syndrome (Deo et al., 2004). Higher levels of MCP-1 were associated with higher age, Caucasian race, early onset of coronary heart disease, smoking, hypertension, hypercholesterolemia and higher hsCRP levels (Deo et al., 2004). Similar association was found in the group of patients with detected calcium in coronary arteries.

It was found that CCR2  $-/-$  mice show smaller area of infarction after ischemic-reperfusion injury, what correlated with decreased oxidative stress of their leucocytes (Hayasaki et al., 2006). So it seems that CCL2/CCR2 axis plays an important role in post-ischemic and post-reperfusion inflammation and could become a new therapeutic goal in selected cardiovascular diseases as well as in stroke in future. It is assumed that CCL2/CCR2 axis inhibition disrupts ischemic-reperfusion injury by decreasing edema, leucocyte infiltration and expression of inflammatory mediators (Dimitrijevic et al., 2007). However, the studies of Tarzami et al. showed that MCP-1/CCL2 played a dual role in myocardial ischemia – beside chemotaxis it also protected myocardial myocytes from hypoxia induced death (Tarzami et al., 2002, 2005). Nevertheless, there is a difference in the role of inflammation in acute and later stages of pathological process (Rosas 2007).

Vascular inflammation plays a central role in atherosclerosis and inflammatory biomarkers, such as CRP, IL-6, MCP and sICAM predict risk of cardiovascular disease (Dupuis et al., 2005). Thus finding genes that influence systemic levels of inflammatory biomarkers may provide insight into genetic determinants of vascular inflammation and cardiovascular disease.

## 6. Conclusion

Biomarkers of vascular inflammation have genetic, inflammatory and environmental determinants. Identifying genes influencing inflammation, environmental determinants, their interrelationships and early inflammatory biomarkers could help us to improve our understanding of pathophysiology and subsequently carefully consider eventual use of anti-inflammatory agents.

## 7. References

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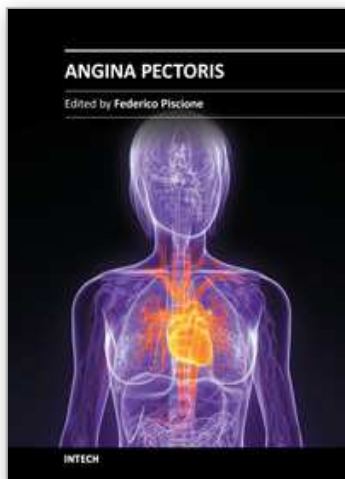
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