

Inflammation in Atherosclerosis and Other Conditions: A Response to Danger

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Key Words

Innate immunity · Danger model · Atherosclerosis risk factors · Atherosclerosis treatment · Statins

Abstract

In the last few years atherosclerosis has been recognized as an inflammatory process. Assessment of low-grade inflammation with indexes like C-reactive protein (CRP) is considered indicative and potentially predictive for this disease. On the other hand, in a large number of clinical studies, a grade of microinflammation has been found to be associated with numerous other processes that may be directly, indirectly or not related to atherosclerosis. The most interesting finding these studies have yielded is that innate immunity is activated in various, previously unexpected, conditions. This phenomenon is better explained by the application of a recently proposed immune activation mechanism, namely, the 'danger model'. It seems that many conditions related to metabolic or homeostatic stress or to pro-atherosclerotic and pre-diabetic dysfunctions, established atherosclerosis or diabetes, but also other early tissue injury – like renal, pulmonary or connective tissue – and several exogenous stimuli, constitute 'danger signals' that induce inflammation which interacts with and complicates the above-mentioned processes. On this basis the complex

relationships between CVD risk factors, atherosclerotic process, other tissue injury and inflammation is examined. The practical application of this hypothesis, namely the new clinical use of CRP as a sensitive – although not specific for atherosclerosis – index of low-grade inflammatory activity as well as to the atherosclerosis treatment are also discussed.

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Introduction

Atherosclerotic cardiovascular disease (CVD) is a major cause of morbidity and mortality, worldwide. Establishing the principal risk factors for this entity is of great importance. Recently, atherosclerosis has been recognized as an inflammatory process [1]. Several experimental data support this concept. Furthermore, serum inflammatory indexes are emerging as CVD risk markers. Among them, C-reactive protein (CRP) is potentially the best candidate [2]. It has been proposed that baseline CRP measurement – reflecting inflammatory activity in the arterial wall – could accurately predict atherosclerotic events that will be apparent many years later [2] but recently, a large clinical study reconsidered the strength of this acute phase protein for the prediction of CVD events [3].

In this text, a hypothesis is formed, based on the results of clinical studies correlating the presence of low-grade inflammation to various conditions – and not only to atherosclerosis – and on a recently proposed immune activation mechanism, namely the ‘danger model’. Furthermore, CVD risk factors and atherosclerosis-inflammation relationships are re-evaluated according to this hypothesis. Finally, the consequences of this proposal in everyday clinical practice, and more specifically the influence of CRP measurement on atherosclerosis treatment modalities are discussed.

Innate Immunity Activation: The Most Important Finding in Clinical Studies Investigating Low-Grade Inflammation

Using highly-sensitive methods – which lowered the detection limit down to 0.1 mg/l – for CRP measurement, we were able to investigate, ‘in mass’, with an easy, stable and relatively cheap method, low-grade inflammation in a series of conditions. Conditions related to metabolism, to initial tissue dysfunction-injury, to diverse neurological or psychological disturbances or to environmental and diet-related factors (table 1) – that we had not previously expected to correlate with inflammation but which are now increasingly being associated with such a process as well as with low-grade activation of the innate immune response. This discovery is probably even more important than the inflammation-atherosclerosis correlation, because: *a degree of immune response is present in a wide variety of conditions characterized by homeostatic stress and initial tissue dysfunction-injury.*

The conditions listed in table 1 which are associated with low-grade inflammation are related to situations that lead to *disturbance of endogenous factors* and not to the consequences of an exogenous invasion (e.g. an infection). It is probably difficult for this immunological activation to be satisfactorily explained by the dominating today immunological model (based on self/non-self recognition) which is oriented mainly to the distinction between infectious non-self and non-infectious self [4].

A recently proposed immunological theory, the ‘danger model’ [5], seems to explain more convincingly this phenomenon. This model suggests that ‘the immune system is more concerned with damage than with foreignness, and is called into action by alarm signals from injured tissues, rather than by recognition of non-self’ [5].

Many endogenous natural or modified molecules could act as pathogen-associated molecular patterns (the anti-

Table 1. Correlations between low-grade inflammation as assessed by CRP measurement with high sensitivity methods and diverse conditions (except atherosclerosis). CRP as a predictive index

Increased levels

Metabolism-related conditions

- Obesity (assessed by body mass index or other anthropometric measures)
- Disturbances of glucose metabolism (insulin resistance, elevated fasting insulin, diabetes)
- Disturbances of lipid metabolism (low high-density lipoproteins, low apolipoprotein I, small dense low-density lipoproteins, hypertriglyceridemia)
- Metabolic syndrome

Hypertension

Pulmonary function-related conditions (forced expiratory volume decreases, moderate chronic obstructive pulmonary disease, restrictive lung diseases, obstructive sleep apnea)

Chronic kidney disease (early stages)

Periodontal disease

Neurological-psychological disorders (dementia, decreased cognitive performance, depression, exhaustion, adverse psychological work characteristics, frailty, post-traumatic stress, acute nicotine abstinence)

Heart disorders (atrial arrhythmias, abnormal electro-cardiographic T-axis)

Social and lifestyle-related conditions (low socioeconomic status, non-attendance at religious services)

Smoking (and smoking patterns)

Strenuous exercise

Medications/drugs (hormone replacement therapy – oral but not transdermal, contraceptives, chronic cocaine use)

Diet-related factors (chronic high glycemic load, post-challenge glycemia, dietary glycotoxins, heat-generated advanced glycation end products (AGEs), low diet-derived antioxidants, high-protein diets)

Environmental factors (particulate air pollution)

Age

Decreased levels

Weight loss

Increased physical activity

Moderate alcohol consumption

Medications (statins, fibrates, niacin, β -blockers, metformin, tamoxifen at low doses, nitroglycerin transdermal)

Conditions predicted by subtle CRP increases

Atherosclerosis, diabetes type 2

Potential predictor of other conditions

Weight gain, metabolic syndrome, cancer (little evidence), hypertension, atrial fibrillation

gens postulated to activate immune response), capable of activating the innate and adaptive immune response. Heat-shock proteins are such well-recognized molecules, using Toll-like receptors 4 as pattern recognition receptors in cells initiating immune activation [6]. As was re-

cently shown, CRP itself – a distal inflammation product – could act as such a receptor, participating in oxidized LDL recognition [7] (in this case having the role of a pathogen-associated molecular pattern), a process that may further modulate the immune response [8]. Studies showing that injury itself primes the innate immune response [9] and that simple molecules can act as danger signals [10] are accumulating.

Even in some tissue dysfunction conditions related to atherosclerosis or diabetes (shear stress in hypertension, endothelial dysfunction, or tissue insulin resistance, conditions that are known to be associated with inflammation [11–13]) such endogenous danger signals might be emitted. The persistence of these dysfunctions might lead to initial transient organic injury and finally to definite injury like atherosclerosis or diabetes. In every stage, tissue dysfunction or injury could feed an immune activation. Although initially protective, inflammation may participate in and aggravate tissue injury in later stages.

The ‘dual face’ of inflammation is also evident by the CRP physiologic-pathophysiologic roles: the first is well known (binding and opsonization of microbiological materials, clearance of apoptotic and necrotic materials etc. [14]) while the latter is increasingly becoming evident from the results of recent studies [15]. It is of interest that a number of studies [16–18] – but not all of them [19] – have recently shown that CRP is produced not only in the liver but in other tissues as well; if valid, this later production, as a consequence of local tissue stress, may fit well with the suggested role of CRP as an endogenous danger (or danger-signaling) molecule.

CVD Risk Factors – Atherosclerosis-Innate Immunity (Inflammation) – Relationships

Based on the above data and on the assumption that the ‘danger model’ is valid, a hypothesis based on the complex relationships between innate immunity activation – inflammation – CVD risk factors – atherosclerosis (or equivalent injuries) and other conditions could be formed (fig. 1).

Regarding the danger model application, and although this theory accepts tissue injury as the main source of danger signals, homeostatic stress as well as tissue dysfunction are considered (fig. 1) as separate danger signal generating conditions. This shift of danger signal emission toward earlier stages of injury is based (a) on the well-known correlation between obesity and inflammation [20]; in this case although only a hypertrophic and

supra-functioning but not injured tissue exists, innate immunity is activated (b) on the modulating role of the nervous system in the inflammatory response [21] and (c) on the immunological response known to be activated by modified lipoproteins or other molecules and oxidative stress [22].

Stress conditions as well as tissue dysfunction are transient, however the repetitive and persisting nature of environmental (nutritional, lifestyle or psychosocial) factors, as well as the influence of the genetic background are decisive in establishing an irreversible injury. In analogy, immune response and inflammation initially make an attempt to limit the injury but its continuous activation further complicates homeostatic stress, tissue dysfunction and injury. Inflammation is also important in established injury; the vulnerability of the atheromatous plaque is dependent mainly on this process [23]. Innate immunity activation due to other causes (other tissue injury or exogenous danger signals) may act as an additive aggravating factor (the direct atherogenic potential of some pathogens like *Chlamydia pneumoniae* cannot be excluded [24]), via inflammation, to the whole atherosclerotic process.

Diabetes seems to be not only a clinical equivalent of atherosclerosis but also an equivalent in terms of pathogenesis [25]. Other equivalents might be the metabolic syndrome and obesity [26, 27].

The genetic background seems to influence all of these processes. Baseline levels of CRP in particular, show a heritability of up to 40% in family studies [28] and a CRP gene polymorphism has been shown to not only influence the baseline level of this protein but also the strength of the inflammatory response to diverse stimuli [29]. This latter finding, if confirmed, might be of importance in atherogenesis and will further underline the importance of the genetic factor in the initiation and progression of this entity.

It must be emphasized that other processes, besides atherosclerosis and diabetes, may have similar relationships to innate immunity response and inflammation. CRP measurement predicted the appearance of cancer [30, 31] and of atrial fibrillation [32]. If similar studies appear in the future, correlating low-grade inflammation to other entities, unrelated to atherosclerosis, this will probably mean that a degree of immune activation precedes or correlates to more, hitherto unexpected conditions. The fact that we are focused on atherosclerosis-related – directly or indirectly – conditions and we are not equally focused on other fields, is obvious.

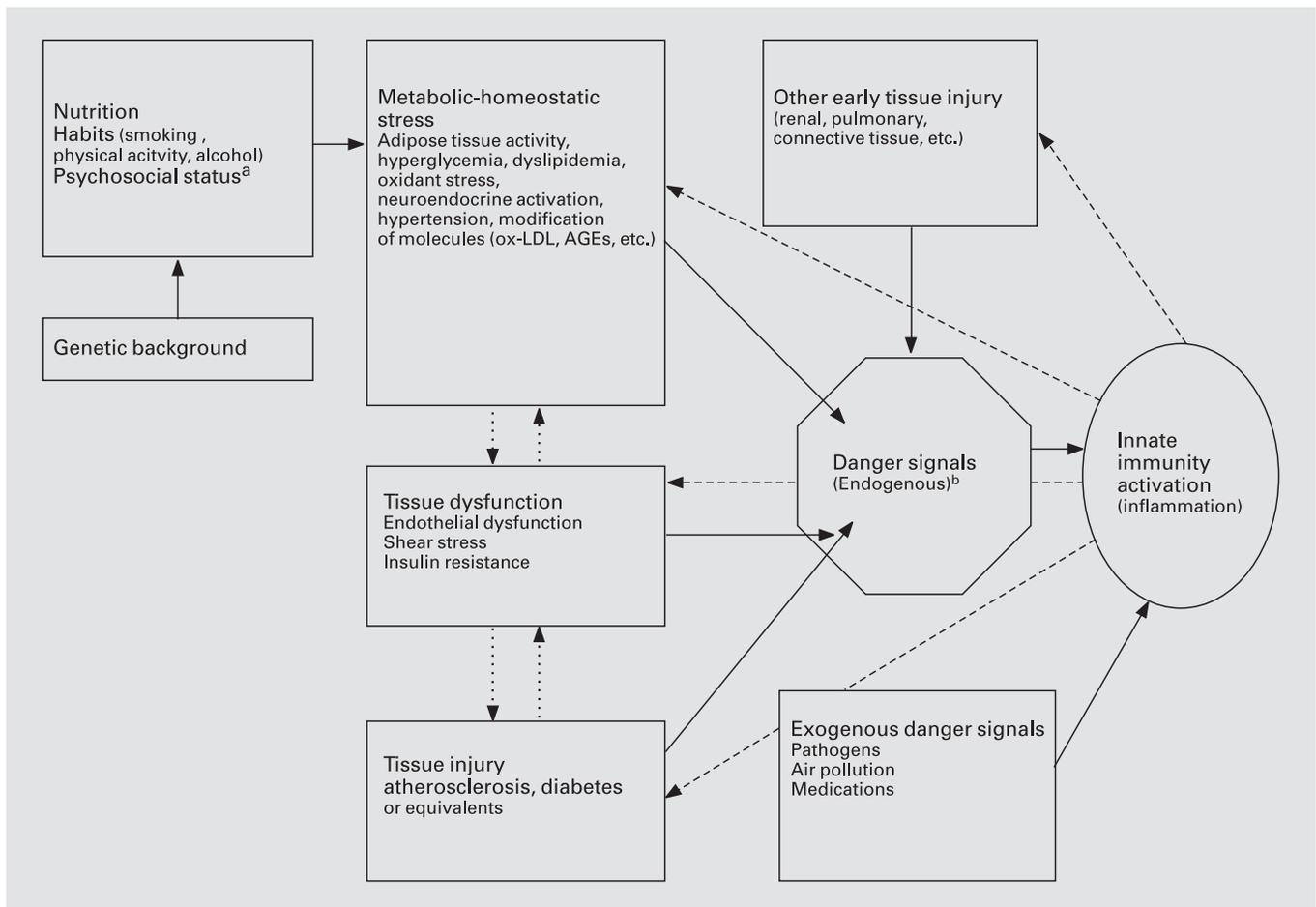


Fig. 1. Inflammation, CVD risk factors, atherosclerosis (or equivalent injuries) and other conditions. ^a Psychosocial status: psychological, work, social, stress-inducing conditions. ^b Potential endogenous danger (or danger signaling) molecules: heat-shock proteins, CRP, complement or others.

Inflammation: A Secondary but Aggravating Factor for Atherosclerosis

In the case that the inflammation-atherosclerosis relationships depicted in figure 1 are valid, low-grade inflammation is a secondary phenomenon due to factors that induce atherosclerosis – and they are the already known ‘traditional ones’ [33] and the disturbances which they provoke in homeostasis – to atherosclerosis itself, to other early tissue injury (like renal, pulmonary, connective tissue) and to exogenous factors (like air pollution or pathogens which induce subclinical infections).

The possibility that inflammatory activity is itself a primary risk factor for atherosclerosis, as numerous *in vitro*, and a few *in vivo* experimental studies have shown [15], has not been convincingly proven in clinical studies.

Although in a recent epidemiological study systemic infection-related inflammation coincided with acute atherosclerosis complications, the absence of data on traditional atherosclerotic risk factors in the population examined does not permit a clear conclusion [34]. Moreover, although a very interesting study showed recently that acute infection in childhood is, transiently, associated with impaired endothelium-dependent vasodilatation [35], it is well known that children – in which traditional atherosclerotic risk factors are usually absent – do not present atherosclerotic complications. This latter fact underlines on the one hand the importance of the presence of the traditional atherosclerotic risk factors, and on the other hand the necessity of the persistent – or potentially of the repetitive or of the additive – and not of the transient presence of inflammation in the development of the

complications of a chronic disease, such as atherosclerosis is.

The fact that populations with high atherosclerosis morbidity such as patients with renal failure, rheumatoid arthritis or chronic pulmonary diseases also have higher microinflammation levels, most likely shows that innate immunity is constantly activated by the specific tissue injury (renal, pulmonary, etc.) that acts as a 'danger signal'. Co-morbidities such as hypertension, oxidative stress, dyslipidemia or already established atherosclerosis or diabetes are more frequent in these patients than in the general population and might also act as a source of low-grade inflammation. The extra inflammation activated by these processes accelerates the appearance of atherosclerosis and its complications, interacting with and aggravating metabolic-homeostatic stress factors, tissue dysfunction and established injury, and might be an explanation for the higher CVD morbidity and mortality in these selected populations. Infections are also more frequent in these patients and are a common cause of true (high-grade) inflammation that interacts with the above factors producing the same result [36].

The New Clinical Use of CRP Measurement Is Close to the Traditional One

The traditional clinical use of CRP is that of a marker indicating the presence and intensity of an infectious, traumatic, neoplastic or connective tissue disease activity [14]. It is very useful for follow-up and evaluation of the response to treatment of these conditions, but its specificity is very low. Its measurement cannot be helpful for the distinction of a specific cause that provoked the inflammatory activity.

It seems, paradoxically, that the new clinical meaning of the CRP (measured by a high sensitivity method and within a range of values between 0.1 and 10 mg/l) as a marker of low-grade inflammation is similar, in an extended sense, to the traditional one. It shows the low-grade activation of the innate immunity by diverse conditions: atherogenic and diabetes-predisposing conditions, prodromal tissue dysfunction and established atherosclerosis/diabetes (or other pathogenetic equivalents), other early tissue injury – renal, pulmonary, connective tissue – or exogenous factors like pathogens, medications and air pollution. *It reflects the grade of an individual's health aggravation by numerous dangerous processes and early tissue injuries, capable of activating innate immunity at a low-grade level.* CRP is a very sensi-

tive marker of the number, of the additive effect, of the intensity and potentially of the response to treatment – or to the modification – of the factors (and probably of others) that table 1 and figure 1 show. Accurate estimation of microinflammation, which needs serial measurements of CRP [37], shows 'the grade of danger' to which an individual is exposed because of the presence and activity of these factors.

The specific causes that provoke low-grade innate immune activation is very difficult to be identified by CRP measurement. Hence, the specificity of CRP, in its new clinical use, is very low and similar to the traditional one. Potentially, this is the cause for the low predictive value for atherosclerosis of this molecule depicted, and confirmed recently [38], in the largest study done so far in this research field [3].

Atherosclerosis Treatment According to the Proposed Hypothesis

The debate for the 'only 50% myth' (only 50% of the patients suffering from an atherosclerotic complication have the traditional CVD risk factors) has recently been rekindled [33]; 80–90% of the patients who had experienced a fatal coronary heart disease event had had at least one of the four major CVD risk factors – smoking, diabetes, hypertension or hypercholesterolemia [33].

Figure 1 shows the factors related to nutrition, to individual habits and to psychosocial status influenced by the genetic background that are the initiating-decisive ones for metabolic-homeostatic stress, tissue dysfunction and injury. In analogy, the same factors feed innate immune activation via danger signals emitted by the dysfunctioning or injured tissues. Accordingly, the main target for atherosclerosis treatment has to be these well-known factors.

Medications that interfere with the consequences of the factors mentioned above which concomitantly have an anti-inflammatory – or immunomodulating – activity are potentially the best for treating atherosclerosis. Statins and angiotensin-converting enzyme inhibitors have such properties. The former correct dyslipidemia while the latter lower blood pressure and concomitantly attenuate oxidative stress, endothelial dysfunction and inflammation. Combating two important atherogenic factors at the same time attenuates the harm induced by these factors and the innate immunity activating danger signals emitted by them. Statins in particular, by modulating the activity of small GTPases, may influence crucial processes

like the production of reactive oxygen species via NADPH-oxidase activation [39] and circulating cells migration to a dysfunctioning or injured tissue during an inflammatory or any immunological event [40]. They are thus acting in a multipotent mode for the interruption of the vicious circle established between immune response and atherogenous factors.

The modification of the traditional risk factors for atherosclerosis remains our first priority. When however this attempt becomes unsuccessful, medications with complex-pleiotropic properties should be employed for treating this pathogenetically complicated disease.

Conclusions

Activation of the low-grade innate immune response and inflammation is implicated in the entire atherosclerotic process but not only. Pro-atherosclerotic conditions like metabolic-homeostatic disturbances, pro-atherosclerotic and pre-diabetic tissue dysfunction, atherosclerosis

and diabetes, other injury (renal, pulmonary, connective tissue) and exogenous stimuli initiate and maintain this activation. Inflammation as a response to danger emitted by these conditions intervenes, complicating and aggravating their evolution. Estimation of low-grade inflammation by CRP reflects the number, the intensity and potentially the response to modification of these processes. It is a sensitive marker of their presence but does not reveal the specific cause that provoked innate immune activation. Atherosclerosis treatment has to be focused on the well-known initiating traditional risk factors and on medications like statins that in addition interrupt the vicious cycle between the dangerous consequences of these factors and the immune response.

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