Chronic Systemic Inflammation Leading Eventually to Myocardial Infarction, Stroke, COPD, Renal Failure and Cancer is Induced by Multiple Risk Factors

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Chronic systemic inflammation is implicated in the pathogenesis and progression of various inflammatory diseases including cardiovascular disease, stroke, lung diseases, renal failure and cancer. Multiple risk factors, in addition to hypercholesterolemia, have been reported in the recent literatures which are responsible for the generation of chronic inflammation in various organs. There are five major risk factors that can be identified with relative specific markers including abdominal fat, dyslipidemia, bacterial and viral infection, hyperglycemia and hyperhomocysteinemia. Many minor risk factors such as pollutant, stress, diet and drugs etc. have also been reported. Though not highly publicized these minor risk factors are also playing important role in their impact of chronic inflammation. These minor risk factors are not identified with specific markers; however, multiple inflammation markers such as urinary microalbumin, homocysteine, uric acid and 3-nitrotyrosine are useful for detecting their presence and monitoring the success of treatment.

Key words: Chronic systemic inflammation, fatal disease, risk factors

Introduction

It has been recognized in recent years that the chronic systemic inflammation is the major cause of all severe and fatal inflammatory diseases [1] including myocardial infarction (MI) [2,3], stroke, renal failure [4], chronic obstructive pulmonary disease (COPD) [5] and cancer [6]. Increasing number of reports in the recent literature have pointed out that the chronic inflammation has to do not only with the pathogenesis (onset of disease) of many inflammatory diseases but also the disease progression and leads eventually to fatal consequences. Conceivably the continuous presence of the risk factor(s) will allow the early acute inflammatory response to propagate down-stream resulting in the generation of a sequence of events and leading eventually to oxidative and nitrosative stress. Given sufficient time the chronic inflammation may also spread systemically causing the onset of many severe, fatal inflammatory diseases at the same time.

The impact of chronic inflammation on disease pathogenesis was first recognized from the study of the onset of atherosclerosis (atherogenesis). Chronic inflammation taking place in the coronary artery leads eventually to the foam cell formation, the formation of plaque in the blood vessel and atherosclerosis [2]. Earlier, cholesterol was suggested as the major (if not the only) causative factor of atherosclerosis. Since not all subjects with MI were associated with elevated cholesterol it was later realized that inflammation especially the chronic inflammation is the primary driving force which is responsible for the onset of atherosclerosis. It was also discovered later that the risk factor(s) that induces chronic inflammation is not limited to hypercholesterolemia. Many additional risk factors exist that they will also induce chronic inflammation [3]. In fact, we now realized that the chronic inflammation may simul-
Chronic systemic inflammation and risk markers

taneously leads to multiple clinical complications as manifested in various severe inflammatory diseases involving heart, kidney and lung.

Conceivably, detection and removal of these risk factors are most important not only to prevent the onset of chronic inflammation but also the initiation of various severe and fatal diseases.

**Traditional Risk Factors**

In the past, hypercholesterolemia was considered as the major risk factor for the initiation of atherosclerosis. Several other risk factors have also been recognized even though their exact mechanisms of risk were not clear.

- a) Hypercholesterolemia
- b) Positive family history
- c) Cigarette smoking
- d) Obesity
- e) Sedentary lifestyle
- f) Stress

The importance of cholesterol in atherosclerosis has been highly publicized in the past. The public was under the impression that reduction of cholesterol and quitting smoking are most critical in preventing heart attack (AMI)

**Major Risk Factors, Better Defined**

We now have realized that there are multiple risk factors which may be more or equally important as hypercholesterolemia [3] for the onset of atherosclerosis. All these risk factors mediate their impact on atherogenesis through the induction of chronic inflammation (Scheme 1). These include abdominal obesity, dyslipidemia, hyperglycemia, bacterial and viral infection and hyperhomocysteinemia. They all can elicit chronic inflammation and lead eventually to various inflammatory diseases

**Abdominal Obesity**

Abdominal obesity or central adiposity (not the overall obesity as was known before) is now being recognized as one of the risk factors and could be the most important risk factor inducing chronic inflammation [7]). Pro-inflammatory cytokines, such as interleukin 6 (IL-6) and tumor necrosis factor-alpha (TNF-α) are known to be generated from abdominal fat and cause the initiation
and propagation of sequential events associated with chronic inflammation.

In addition to the generation of proinflammatory cytokines, adipose tissue is now being considered as an active endocrine and paracrine organ capable of secreting novel cytokine-like molecules, collectively termed adipocytokines. Among adipocytokines, leptin and adiponectin are two hormones that have closer relationship with obesity. Excess abdominal fat is associated with elevated level of plasma leptin but decrease level of adiponectin.

**Bacterial and Viral Infection**

It is now being recognized that the chronic inflammation may also be induced by bacterial and virus infection [8]. Much interests have been focused on infection by a bacteria, named *Chlamydia pneumonia (C. pneumonia)*, and its contribution to atherogenesis. Increased concentration of soluble inflammation markers has also been consistently reported in HIV-positive patients. Detection of autoantibodies against *C. pneumonia*, cytomegalovirus, and *Helicobacter pylori* have been regarded as the major risk markers for heart disease associated with infection.

Since it is technical difficult to detect the presence of bacteria and virus directly in the blood circulation, therefore, the identification of the presence of pathogens may be possible by measuring autoantibodies against these pathogens. Measurement of viral DNA in the blood circulation could be the alternative of detecting viral infection. Future investigation is needed for the development of this technique.

**Dyslipidemia**

Dyslipidemia or abnormal lipid profile, particularly the elevation of low-density lipoprotein associated cholesterol (LDL-C) and triglyceride, is one of the risk factors that will induce chronic inflammation [9]. The traditionally recognized risk factor, namely hypercholestolemia, is one of the abnormalities included in the abnormal lipid profile.

**Hyperglycemia**

Proinflammatory cytokines can also be generated from hyperglycemia (elevated serum glucose) causing the initiation and propagation of chronic inflammation as in patients with type 2 diabetes [10]. The risk of hyperglycemia is most likely due to the increased production of reactive oxygen species by autooxidation of excess concentration of serum glucose.

It should be noted, as reports from recent investigations have pointed out, that the glucose-derived advanced glycation end products (AGE) may play a more important role in inducing chronic inflammation than that of the elevated serum concentration of glucose [11]. AGE could be a more important biochemical abnormality and has been found to be largely responsible for the development of additional clinical complications such as renal failure and cardiovascular disease (CVD) in type 2 diabetes.

**Hyperhomocysteinemia**

Hyperhomocysteinemia has been known to generate oxidative stress and induce chronic inflammation [12]. It appears that generation of reactive oxygen species (ROS) by these risk factors described above is the major cause of inflammation [13]. Inflammation starts from the acute inflammatory response. If these risk factors are not removed and continue to exist, the acute inflammatory response will develop into chronic inflammation and the development of the sequential inflammatory events will follow and lead eventually to oxidative and nitrosative stress.

**Miscellaneous Minor Risk Factors**

Many less publicized minor risk factors for chronic inflammation have attracted increasing attention in recent years. Because they do not associated with specific markers, therefore, are not easily to be identified. They are also not in general under our control making the study of their impact more difficult. However their impact on chronic inflammation and the development of clinical complications become more and more important because of the increasing pollution of our environment and the increased pressure and stress we face in our daily life.

**Pollutant**

Epidemiological studies have associated the increase of respiratory and cardiovascular mortality and morbidity with high levels of air pollution particulate matter. Population-based studies suggest that the appearance of inflammation markers and the risk of coronary heart disease (CHD) are associated adversely with environmentally relevant pollutants [14]. The risk of asbestos on chronic inflammation should also not to be ignored [15].
Chronic systemic inflammation and risk markers

Stress

There are ample evidences indicating a link exists between psychosocial stress and the presence of chronic inflammatory reactions. These inflammatory reflexes might be of major influence not only for metabolic and vascular disease such as CVD but also for many autoimmune diseases for which stress has been reported as a risk factor [16].

Diet

Diet is also known to link to the risk of coronary heart disease, sudden death, and type 2 diabetes. For example, we have realized recently that trans fatty acids not only affect on serum lipoproteins, as known in the past, but impact also on the induction of chronic systemic inflammation and the pathogenesis of atherosclerosis, acute coronary syndromes, sudden death, insulin resistance, dyslipidemia, and heart failure [17]. Caloric restriction (CR) has been reported to be effective in reducing oxidative stress during diabetes, and in moderating the expression of some markers of inflammation [18]. Excess iron in the diet has been known to promote oxidative stress and inflammatory response in animals and the development of chronic kidney disease [19].

Alcohol and Drug Abuse

Excess use of alcohol has been known as a major cause of cerebrovascular and cardiovascular disease in young adults [20].

Medication

We need to pay attention to the medications that we are taking. For example, the use of tamoxifen as a breast cancer preventive agent has been found to raise inflammation marker such as C-reactive protein (CRP) and an increased risk of endometrial cancer and venous thromboembolic events, particularly in postmenopausal women [21].

Exposure in Mining

Chronic mercury exposure, the long-term occupational exposure to mercury could be one of the risk factors for increased lipid peroxidation and increased mortality related to ischemic heart disease found among the mercury miners [22].

Autoantibody

Autoantibodies, as detected in many autoimmune diseases, could also be the risk factor inducing chronic inflammation. The association between autoantibodies and the chronic inflammation may explain why chronic inflammation is frequently detectable in patients with various autoimmune diseases. Understanding this relationship is believed that will shed light in their treatment (such as in immunomodulatory therapies and immunosuppression) [23].

Risk Factor(s) Detection

Identification of Specific Risk Factor

As mentioned above that the chronic inflammation will develop from the acute inflammatory response due to the persist presence of risk factor(s). In other words, removal of the risk factor(s) will prevent the continued progression of acute inflammatory response to the subsequent serial inflammation events and the production of oxidative and nitrosative stress. The list in Table 1 has suggested markers that will aid in the identification of these major risk factors and hence monitoring their removal. These markers can also be used to monitor the success of treatment aiming at eliminating these risk factors.

Panel of Multiple Markers of Inflammation

For many of those minor risk factors there are no specific markers known for their identification. In this case monitoring multiple inflammation markers may help

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Associated Circulating Marker</th>
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<tbody>
<tr>
<td>Bacterial and viral infection</td>
<td>Autoantibody against pathogen, plasma viral DNA</td>
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<tr>
<td>Abdominal obesity</td>
<td>Leptin, adiponectin</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>Lipid profile (triglyceride, LDL-cholesterol)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>HbA1c, advanced glycation end products (AGE)</td>
</tr>
<tr>
<td>Hyperhomocysteinemia</td>
<td>Isma total homocysteine</td>
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identify their presence and the success of their elimination. Multiple inflammation markers such as urinary microalbumin, serum uric acid, plasma homocysteine and plasma 3-nitrotyrosine could be used.

References

慢性全身性發炎反應，被認為涉及多種發炎疾病如心血管疾病、中風、肺病、腎衰竭及癌症的致病機轉及其病程進展。在最近的文獻中多種危險因子，除了高膽固醇外，已被報導會引發不同器官之慢性發炎反應。目前有五種主要的危險因子可被相關的生物標記偵測出其存在與否，包括中廣型肥胖、高血脂、細菌及病毒性感染、高血糖及高半胱氨酸症。許多次要之危險因子如空氣污染、壓力、飲食及藥物等亦曾被報導。雖然這些次要的危險因子還未被高度認同，但在引發慢性發炎中仍扮演重要角色。這些次要危險因子目前還無法以專一的標記偵測出，然而有多個發炎指標如尿液微白蛋白、半胱氨酸、尿酸及硝基酪氨酸等可偵測出危險因子的存在並可追蹤治療的成功與否。

關鍵詞：慢性全身性發炎反應、致命疾病、危險因子

綜論

由多重危險因子所引發之慢性全身性發炎反應，最後會導致心肌梗塞、中風、慢性阻塞性肺病、腎衰竭及癌症

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關鍵詞：慢性全身性發炎反應、致命疾病、危險因子