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New understanding on the pathogenesis of acute arterial thrombosis

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Acute myocardial infarction (AMI) is a typical arterial thrombotic event. Acute arterial thrombosis is a common disease with high morbidity worldwide. The sites at which the thrombus forms tend to be abnormal and patients with arterial thrombosis tend to be younger.[1] Thus, arterial thrombosis has been a social burden and the consequent high morbidity and disability have been a worldwide health problem.[2] The typical pathology of acute arterial thrombosis is the rupture of soft plaque cap in the arterial endarterium, aggregation of platelets at the site of rupture and subsequent thrombosis.[3] Acute rupture of soft plaque cap has been regarded as an initiator of arterial thrombosis.[4] Some investigators speculate that soft plaques are landmines, while what events may trigger the landmine and when the landmine would be triggered are still unclear.[5] The pathogenesis is generally ascribed to the damage of vascular endothelial cells, change in blood flow and increase in the blood coagulability.[6] The rupture of unstable atherosclerotic plaques and the subsequent adhesion and aggregation of platelets at the sites of rupture may trigger the thrombosis.[7] Evidence-based medicine shows atherosclerosis is closely related to multiple risk factors such as hypertension, hyperlipidemia, hyperglycemia, obesity and smoking.[8] However, the clinical phenomenon that acute arterial thrombosis also occurs in population which are not exposed to these risk factors is difficult to explain. Thus, there might be mechanisms other than the above mentioned factors involved in the pathogenesis of arterial thrombosis.

Human genomics has the advantages of wholeness, comprehensiveness and directivity. Although there is difference in the gene-guided protein synthesis among individual proteins which requires to be validated by proteomic and cytological studies, comparisons of gene expression patterns among different groups and functional analysis of differentially expressed genes may provide a general view and a new horizon for the understanding of mechanisms underlying the pathogenesis of diseases. This is a unique feature of genomics.[9,10] In the studies published in the current issue,[11,12] gene expression profiles were compared among patients with AMI (Group A), patients with stable angina (Group B) and healthy controls (Group C). Our findings may provide a new understanding on the pathogenesis of acute arterial thrombosis.

Sample clustering analysis of genes indicated that patients in Group A had a special gene expression pattern. Hierarchical clustering analysis classified genes into several co-expression modules, which displayed the difference in the gene expression pattern among Group A, B and C. Functional analysis of differentially expressed genes showed the genes with significantly down-regulated expression in Group A were related to mitochondrial metabolism, ion metabolism, activation of intracellular bilirubin, regulation of T lymphocyte activity, electron transport chain, MHC Ⅱ receptor activity, regulation of lymphocyte proliferation and transcription. Genes with markedly up-regulated expression in Group A were associated with apoptosis, inflammatory response, functions of macrophages, neutrophil-mediated immune reaction, cell metabolism, cell repair, development of immune system and signaling pathways related to steroid receptors. However, the gene expression patterns were comparable between Group B and C, suggesting the stability of biological metabolism in both groups.

Besides the comparisons of gene expression pattern, the differentially expressed genes related to innate immunity and adaptive immunity were also compared among Group A, B and C, and these genes were related to phagocytes (neutrophils and monocytes), NK cells,[13] complement system, cytokines, adhesion molecules, T cells, B cells, coagulation and anti-coagulation system and fibrinolysis system. Results showed hyperfunction of phagocytes in Group A, reduced killing effect of NK cells, reduced complement-

mediated membrane lysis ability. Increase/decrease in IFN, interleukine (IL), and chemokines. Increase in TNF activity demonstrated the significant imbalance among cytokines. The functions of adhesion molecules were increased, functions of CD3T were reduced. Significant imbalance of CD4 cell function, a shift towards Th1 dominance, reduced killing effect of CD8T cells and disordered B cell function were also observed. In Group A and B, the mRNA expressions of some genes related to coagulation factors were up-regulated significantly, the mRNA expressions of genes related to several anti-coagulation factors in Group A were significantly higher than those in Group B and C. In Group A and B, the mRNA expressions of plasminogen activator inhibitor-1 and urokinase-type plasminogen activator were significantly up-regulated. These suggested that the functions of some coagulation factors and anti-coagulation factors were increased and there was a functional imbalance in the fibrinolytic system.

The immune system generally acts to defense pathogenic microorganisms. Precisely, immune system mainly functions to timely recognize and remove exogenous microbes (such as virus and bacterium) and endogenous malignant cells.[14] The immune function can be divided into innate immunity and adaptive immunity. The innate and adaptive immunity may act synergistically to clear cells with foreign and /or pathological antigens, avoiding the occurrence of diseases. The abnormal immune function may cause infectious diseases, malignant diseases and autoimmune diseases.[15,16]

Participants of innate immunity include phagocytes, NK cells, complement system, and cytokines, and those of adaptive immunity include T cells and B cells. Innate immunity functions can kill the exogenous pathogenic microbes (such as virus and bacterium), which is not specific for a pathogen. Cells of innate immunity may collect information of pathogens and integrate and transmit this information to adaptive immunity. Then, innate immunity and adaptive immunity interact and function synergistically to remove exogenous pathogenic microbes and endogenous malignant cells.[17,18] NK cells and CD8T cells target the cells infected by virus or bacterium or malignant cells, and bind to these cells via adhesion molecules. Then, both NK cells and CD8T cells release perforins and granzymes to kill the abnormal cells.[19,20] Complement system also involved in the innate immunity and adaptive immunity. It may kill pathogenic microbes via membrane attack complex. In addition, the complement system is also associated with immune regulation and mediates humoral immune response.[21] Neutrophils are involved in inflammatory reaction, can release reactive oxygen species, and phagocytize and clear metabolites.[22]

In our reports,[11,12] we presented our findings from human genomics study. Detection of differentially expressed genes showed patients with acute arterial thrombosis developed the collapse of immune defense, suggesting the abnormal immunity. Thus, the immune system fails to timely and effectively remove exogenous pathogenic microbes and endogenous malignant cells. Patients recruited into present study had no malignancies. Thus, we hypothesized that arterial thrombosis is an infection-related disease. The collapse of immune defense is an up-stream event of acute arterial thrombosis (Figure 1). Failure to timely and effectively clear circulating pathogenic microbes in the artery is a cause of inflammatory injury to the arterial endarterium. The damage to arterial endarterium (including the rupture of soft plaque cap) is a consequence of inflammatory reaction, and triggering of adhesion and aggregation of platelets, coagulation, anti-coagulation and fibrinolytic systems is a down-stream event of arterial thrombosis. Psychological and mental stress may facilitate the imbalance of immune function.[23] The activation of sympathetic system may increase the oxidative stress of blood vessel wall, causing the instability of atherosclerotic plaque.[24]

In addition, our results also indicated the functions of some coagulation and anti-coagulation factors were increased and there was imbalance in the function of fibrinolytic system although the immune function was stable in Group B.

In conclusion, the holistic analysis on the basis of genomics study of acute arterial thrombosis suggests that clinicians may use combined immune indicators to screen subjects with risk for arterial thrombosis, and to ease the psychological and mental stress, to mediate the regulation of immune function and to optimize the lipid-modulating therapy, which might be effective to prevent acute arterial thrombosis.

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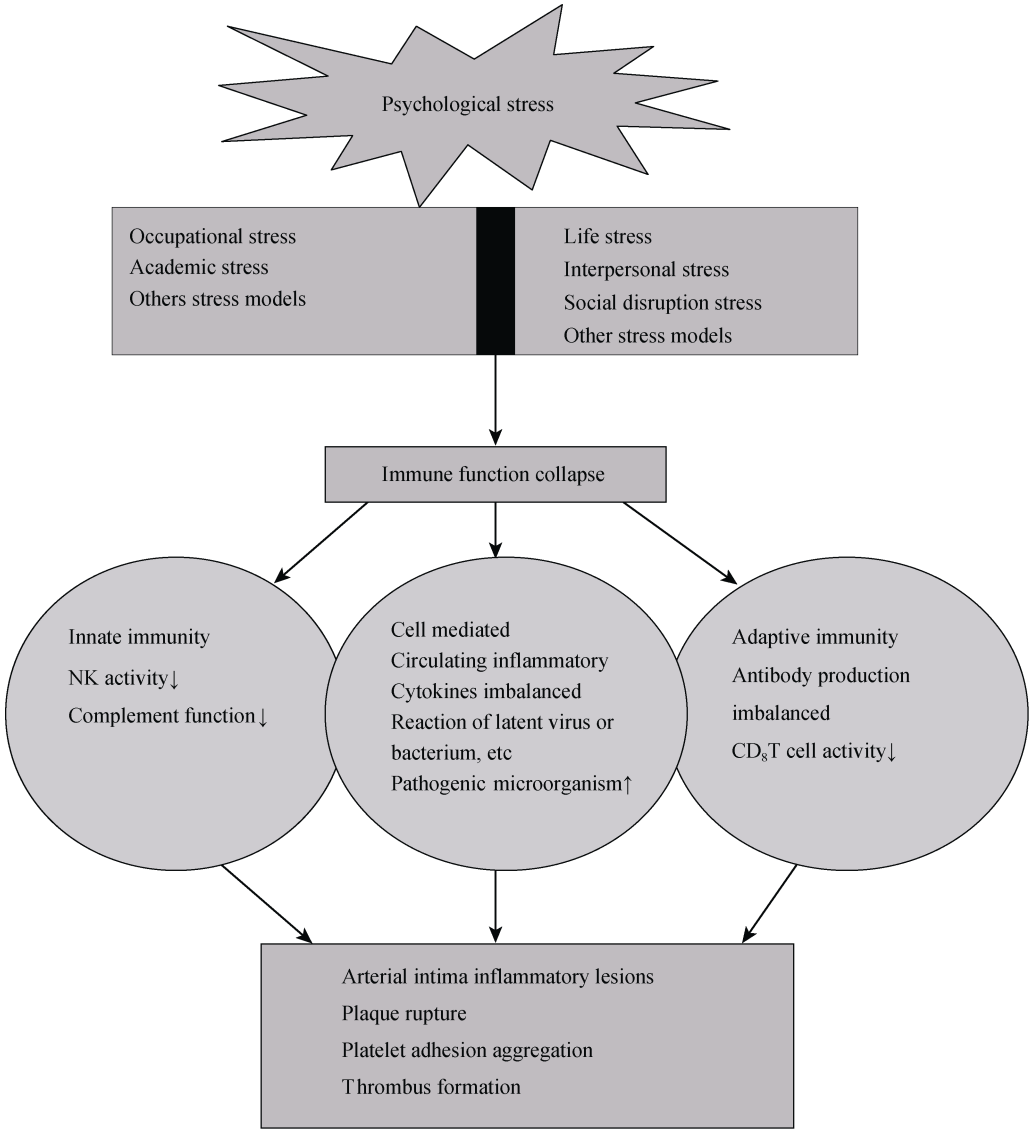

Figure 1. Scheme of our hypothesis. Psychological and mental stress, collapse of immune function, and potential infection of pathogenic microbes may cause inflammatory damage to the arterial endarterium and subsequent rupture of plaques, adhesion and aggregation of platelets, activation of coagulation system and final thrombosis.

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