Biology

Discovery of Disease Susceptibility Genes of Kawasaki Disease and Possibility of Its Clinical Application

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Background of Research

Kawasaki disease is a disease contracted mainly by infants with symptoms of inflammation in medium- and small-sized blood vessels in the entire body. It has been already more than 40 years since its discovery by Doctor Tomisaku Kawasaki in 1967, but its causes are still unknown. Although the cases of the most serious complication of coronary artery aneurysms have been drastically reduced with the administration of high-dose γ-globulin therapy, the treatment of a group of about 15% of the patients who exhibit resistance to the above therapy is still a major issue. On the other hand, it has been clarified from an epidemiological standpoint that Kawasaki disease is a multifactor disorder in which genetic factors are strongly involved, and this clarification has contributed to the expectation that elucidation of the genes related to disease susceptibility can be a major breakthrough in the Kawasaki disease research.

Achievements of Research

We have adopted human genetic research methods targeting the entire genome and thereby found the locations of susceptibility genes on the chromosomes, and then by using that information we have identified the disease susceptibility genes. We selected genetic regions of chromosome No. 4, 7, 12, 19 and X based on the judgment that part of each of the candidates can be promising in finding the responsible genes. As we promoted detailed analysis on them, it has been recently made clear that the inositol 1, 4, 5-triphosphate 3-kinase C (ITPKC) genes in chromosome number 19 is one of the disease susceptibility genes. As a result of subjecting ITPKC to excessive expression and knock-down with the cell line of T cell system, it was found to be conversely controlling IL2, one of the cytokines that cause inflammation. ITPKC is one of the enzymes that phosphorylate IP3 that transmits signals from outside the cell and generate IP4, and it was discovered that one of the roles of ITPKC is to suppress the activation of T cells. Though the gene polymorphism which is supposed to be the cause is located in the first intron, the research revealed that through its intervention with the efficiency of splicing, it is influencing the activation of ITPKC. It was also suggested that this gene polymorphism is possibly involved with the generation of coronary artery aneurysms and resistance to the therapy.

Prospect of Research

For the moment, we are promoting studies for the purpose of clinically applying the acquired indications of whether the gene polymorphism we discovered jointly with pediatricians can actually predict the resistance to γ-globulin therapy and generation of the complication of coronary artery aneurysms as well as whether the suppression of the identified signal communication route can be effective for using cyclosporine which has already been known.