Genetic variations in the NALP3 inflammasome: a susceptibility factor for inflammatory diseases

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Vertebrates possess a sophisticated immune system that helps them not only to fight against a wide variety of microbes but also against non-microbial harmful substances. This ability partly exists from birth, denoted ‘innate immunity’ and is further acquired upon being exposed to the pathogens, in which case it is retained for life, and classified as adaptive immunity. Innate immunity has been intensely studied in the past few decades, and has led to a better understanding of the mechanisms, behind how individuals recognize and respond when exposed to pathogens. Several types of host’s sensors have been identified, each of which is specialized for detecting a particular type of microbe.

Recently a special type of sensor termed as the ‘inflammasome’ was identified, which in addition to microbes, recognizes harmful particles, in the environment as well as inside the body. The inflammasome is made up of three different proteins which upon sensing danger, associate together to form a complex. This complex then responds by producing inflammatory substances, most important of which is Interleukin-1. However, in certain cases the inflammasome complex can erroneously result in inflammation in the host by continuously producing Interleukin-1. An example of the above situation is the genetic alterations in the inflammasome proteins which causes unsolicited Interleukin-1 production, and thereby lead to serious inflammatory outcomes. Patients suffering from such defects are successfully treated with the blockade of Interleukin-1.

We report a patient who had been suffering from severe inflammation for 20 years. Genetic screening of the inflammasome components revealed two variants which may have contributed to his symptoms. Upon treatment with IL-1 blockade the patient showed remarkable recovery from the symptoms and the results from our experimental studies indicated an over-activity of the inflammasome. The two genetic alterations present in this patient occur in approximately 4% of the normal population implying that these individuals
may be more prone to develop inflammatory diseases. We therefore genetically investigated a group of patients with rheumatoid arthritis, which is a joint disease caused by long-term inflammation. We found that the patients, who carried both the genetic variants, were at increased risk for rheumatoid arthritis and required more aggressive forms of treatment. Our results suggest that such individuals could possibly benefit from an early genetic screening and a timely initiation of IL-1 blocking treatment. More studies in other RA groups need to be done to confirm these results.