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# How pathogens have shaped genes involved in our immune system

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(PhysOrg.com) -- A recent study on human genetics on various populations across the world conducted by researchers from the Institut Pasteur and the CNRS (France) has shown how pathogens can shape the patterns of genetic diversity of our immune system over time. Results show that bacteria, fungi and parasites, unlike viruses, appear to have allowed the introduction of mutations in the genes of some proteins of the innate immunity system, thus enabling greater genetic variability. In some cases, these mutations may even constitute an advantage, giving the human host improved resistance to infectious diseases such as leprosy or tuberculosis.

Institut Pasteur and CNRS researchers from the Human Evolutionary Genetics Unit have recently published the results of their research illustrating the influence of the relationship between humans and pathogenic agents in the journal *PLoS Genetics*. The scientists studied the genetic variability of ten proteins of the innate immune system, the first line of host defense against these agents that attack the human organism. These proteins are receptors belonging to a family known as TLR (Toll-like receptors) and are responsible for recognizing pathogenic agents so as to trigger an immune response and eliminate them.

The researchers' work demonstrated an extreme degree of similarity between the genes of virus-recognizing TLRs among the various populations across the world; mutations here are very rare and the sequence of these genes is highly conserved. Viruses have therefore exerted very high selective pressure on these proteins over time by

precluding them to evolving genetically. On the other hand, the genes of the TLRs which recognize bacteria, fungi or parasites exhibit a much higher degree of variability. It is possible for mutations to accumulate within these genes without it proving critical for the organism. This suggests that the role of these proteins is not essential and more redundant.

This research supports previous observations demonstrating that the small number of known mutations affecting the genes of virus-recognizing TLR receptors are at the origin of rare, serious diseases. This is the case for a mutation affecting the TLR3 gene which has previously been identified as being responsible for encephalitis. Mutations affecting the genes of the other TLR types appear to cause or favor less severe, more common infectious diseases. One mutation that affects the TLR6 gene, for example, is known to be involved in susceptibility to asthma in children.

This research also enabled scientists to demonstrate that a mutation affecting TLR1, a receptor responsible for recognizing bacteria, may actually constitute an advantage! This mutation, found in two out of five people in Europe, prevents the expression of this receptor at the cell surface, and consequently reduces the inflammatory response by 40 to 60%. In previous studies, this mutation was even associated with greater resistance to leprosy and tuberculosis.

The evolutionary approach of this research sheds new light on the question of the relationship between humans and pathogens. Based on the direct analysis of genetic sequences, it opens up new possibilities, to be explored from a clinical, immunological and epidemiological point of view, for a better understanding of susceptibility to certain diseases.

More information: Evolutionary Dynamics of Human Toll-Like Receptors and Their Different Contributions to Host Defense, PLoS

Genetics, July 17, 2009.

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