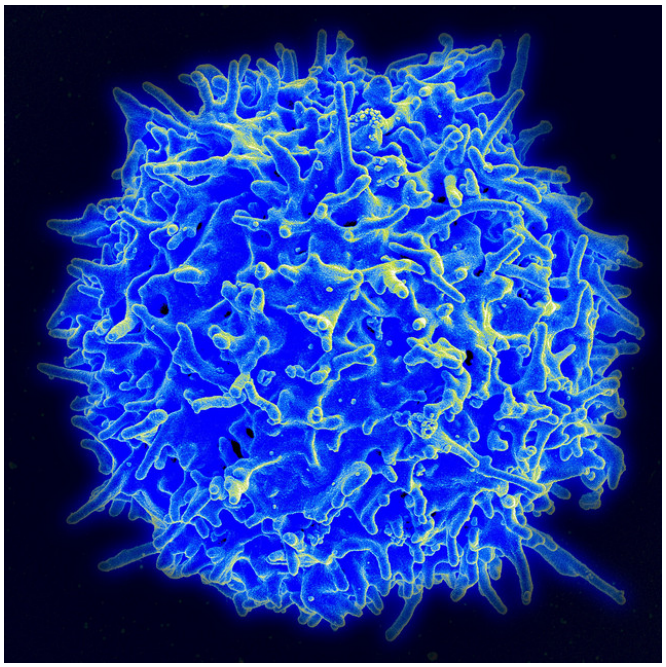
New gene mutations found in white blood cells in patients with rheumatoid arthritis

21 June 2017



Scanning electron micrograph of a human T lymphocyte (also called a T cell) from the immune system of a healthy donor. Credit: NIAID

Gene mutations accumulating in cells are typical of the development of cancer. Finnish researchers have found that a similar accumulation of mutations occurs also in some patients with rheumatoid arthritis.

Gene mutations that accumulate in somatic cells have a significant impact on the development of cancer, yet no studies on their involvement in the pathogenesis of autoimmune diseases have previously been conducted. A research project conducted in cooperation by the University of Helsinki and the Helsinki University Central Hospital found that somatic mutations were present also in patients with rheumatoid arthritis.

Published in the *Nature Communications* journal, the study found mutations in genes important to the immune defence system in white cells separated from blood samples taken from patients recently diagnosed with rheumatoid arthritis.

"It may be possible that these mutations affect the regulation of the inflammatory process," says Satu Mustjoki, a research professor at the Finnish Cancer Institute and the University of Helsinki.

Altogether, 85 patients with recently diagnosed rheumatoid arthritis participated in the study, in addition to which there were 20 healthy control subjects. By utilising the latest deep sequencing techniques, the researchers identified mutations in one-fifth of the patients. All identified mutations were located in cells known as killer cells, or cytotoxic CD8+ T cells. No mutations were found in helper cells, or CD4+ T cells.

"One somatic mutation was found in a single healthy control subject, which means that the finding is not entirely arthritis specific," notes Professor Marjatta Leirisalo-Repo, a specialist in rheumatology.

Mutations only develop in mature T cells

The ability found in T cells to recognise countless protein structures inherent in pathogens is based on their versatile selection of T cell receptors. This selection is formed in the thymus, where gene stubs that code the T cell receptors found in T cells are split and rearranged into functioning receptors. Thus, the surface of each new T cell is imbued with a unique T cell receptor.

When the immune defence system is activated, T cells multiply exponentially while identical T cells form cell clones that can be identified by the rearrangement of their shared, unique T cell receptor.

Enlarged T cell clones were found in all patients

with rheumatoid arthritis concomitant with somatic mutations. Further investigation proved that the mutations were limited to these enlarged cell clones.

"This indicates that mutations are formed only in mature T cells, not at the stem cell level," say BM Paula Savola and PhD Tiina Kelkka, the main authors of the article. "If mutations were formed at the earlier differentiation stage, they would have been present in CD8+ T cells and CD4+ helper cells expressing other T cell receptor types as well."

The mutations were found to be permanent, since identical clones and mutations were found in the patients' white blood cells several years after the original finding.

Are mutations "genomic scars?"

"For now, there is no certainty on how these mutations affect the regulation of chronic inflammations. They may be, for lack of a better word, 'genomic scars' formed as a result of the activation of the immune defence system," says Mustjoki.

"In any case, this research project revealed a new connection on the molecular level between autoimmune diseases and cancer, which brings us one step closer to understanding these diseases."

The starting point for this project was earlier findings related to LGL leukaemia made by Mustjoki's research group. In LGL leukaemia, somatic mutations often found in the STAT3 gene and located also in the cytotoxic T cells of patients cause a slowly progressing blood disorder, in addition to which they predispose patients to autoimmune diseases. The most common autoimmune disease related to LGL leukaemia is rheumatoid arthritis.

"In the future, we intend to study the prevalence of this phenomenon in other inflammatory conditions and the practical significance of these mutations as regulators of inflammatory reactions," says Mustjoki.

More information: Somatic mutations in clonally expanded cytotoxic T lymphocytes in patients with newly diagnosed rheumatoid arthritis. *Nature Communications*. DOI: 10.1038/ncomms15869

Provided by University of Helsinki