Immune cell genome differences underlie individual predisposition to several diseases

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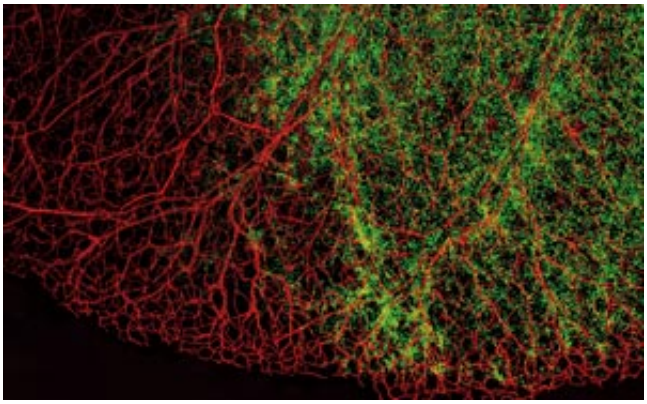

Neutrophil recruitment to site of injury in the skin. Credit: A*STAR Singapore Immunology Network

A new study has found a link between genomic variation and disease susceptibility. An A*STAR-led-team identified certain genomic variations associated with autoimmune, inflammatory and dermatological diseases in a type of immune cell known as neutrophils. These findings shed light on individual susceptibility to several conditions including autoimmune and inflammatory conditions1.

Neutrophils, the most abundant white blood cells in humans, are among the first responders in defense against pathogens—reaching the site of infection and producing inflammatory mediators as little as an hour after infection. How they regulate gene expressions, however, is still unclear.

Olaf Rötzschke of A*STAR Singapore Immunology Network and co-workers have analyzed the neutrophils of 114 healthy individuals of Chinese ethnicity and mapped 21,210 variable genomic locations known as 'expression quantitative trait loci' (eQTLs) scattered throughout the neutrophil genome. These eQTLs contain DNA sequences that vary among individuals and affect the expression level of 832 neighboring genes. "A large number of genes are regulated by DNA regions called eQTLs which are located outside of the coding region of the genes themselves. The variability of eQTLs allows us to understand the biology of health and disease," points out Rötzschke.

The eQTLs influence expression of genes connected with inflammatory responses, immunological diseases and, interestingly, also with dermatological pathologies. "The abundance of eQTLs controlling genes associated with some skin diseases was quite unexpected. This suggests, for example, that epidermal hyper proliferation, characteristic of psoriasis, is promoted also by neutrophils," specifies Anand Kumar Andiappan, first author of the study.

A broader association analysis showed that neutrophils' eQTLs also affect genes involved in 89 additional traits and diseases. In particular, some eQTLs can alter the expression of genes linked with autoimmune conditions, like Crohn's disease, multiple sclerosis and inflammatory bowel disease, among others. Indeed, the same mechanisms of pathogen defense can lead to autoimmune reactions in the case of dysfunctional neutrophils.

Additionally, the eQTLs have a strong impact in the susceptibility of diseases. For example, one variant of the eQTL associated with the gene IL18RAP is connected with the incidence of leprosy, while another variant is associated with the risk for inflammatory bowel disease.

"For a long time, neutrophils have been considered by-standers of the

immune system, now we know that this is very far from true. Collection of eQTLs data from neutrophils gave us a huge amount of information about the role of these cells and showed that neutrophils' dysregulation plays a role in more diseases than we previously thought," concludes Rötzschke.

More information: Anand Kumar Andiappan et al. Genome-wide analysis of the genetic regulation of gene expression in human neutrophils, *Nature Communications* (2015). DOI: 10.1038/ncomms8971

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