Genomics reveals key macrophages' involvement in systemic sclerosis

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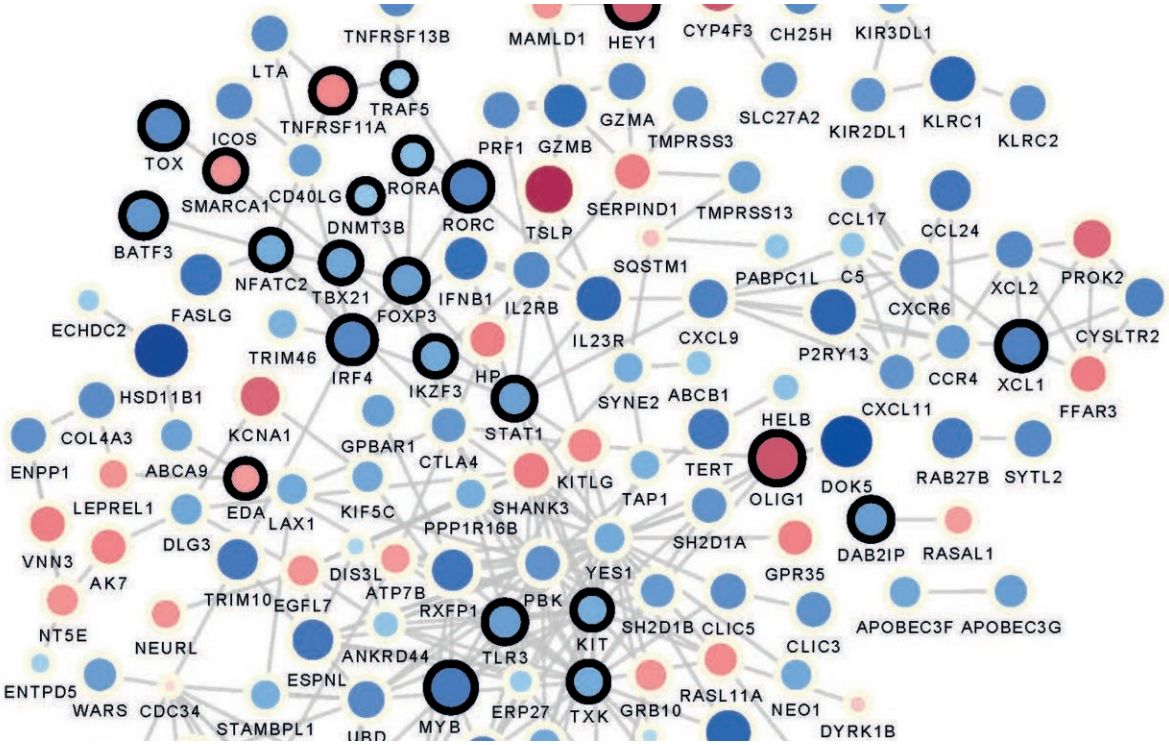

An addition to confirming many genes previously implicated in the genetic predisposition to SSc, the study further discovered hundreds of genes that are previously not known to be associated with disease. This provides a new starting point to better understand the disease aetiology, its genetic causes and develop therapies for SSc. Credit: Duke-NUS Medical School

A new international study has made an important discovery about the

key role of macrophages, a type of immune cell, in systemic sclerosis (SSc), a chronic autoimmune disease which currently has no cure.

The research led by Enrico Petretto, Associate Professor at Duke-NUS Medical School (Duke-NUS), along with Dr Jacques Behmoaras at Imperial College London and collaborators from University College London in the UK, established for the first time a decisive link between immune cells, specifically the macrophages derived from SSc patients and systemic sclerosis. The study also demonstrated the role played by macrophages in the development of the disease due to known genetic factors, such as the case of the sussceptibility gene GSDMA, which has been involved in cell death in the skin and was associated to the disease in 4,436 SSc patients, but whose function in macrophages from SSc patients was unclear.

Previous genetic studies have found various genes associated with SSc susceptibility, but so far, it is not known for certain which type of cells are crucial for the development of the disease. The team used advanced transcriptomic and genetic analyses, which included RNA-sequencing and systems-genetics in macrophages of 57 SSc patients, and established decisively the role for hundreds of macrophage genes in the development of SSc. Their discovery will point the way for researchers looking to develop new therapies for SSc.

"In the long quest for finding therapies for systemic sclerosis, our findings have implications for understanding the genetic basis of the disease, and we believe our discovery will prompt detailed functional studies in macrophages and immune cells, hopefully providing a starting point to develop greatly needed treatments for this disease" explained Professor Petretto, co-lead principal investigator and coordinator of the study.

Published today in the *Annals of Rheumatic Diseases* (ARD)—the

highest ranked journal in *Rheumatology*—in addition to confirming many genes previously implicated in the genetic predisposition to the disease, the study further discovered hundreds of genes that are previously not known to be associated with SSc. This provides a new starting point to better understand the disease aetiology, its genetic causes and develop therapies for SSc.

"Investigating how genetic variation is responsible for systemic sclerosis is a colossal task. By looking at immune cells such as macrophages, we can generate specific hypotheses that will allow us to understand how these cells cause damage," added Dr Jacques Behmoaras, co- lead principal investigator from Centre for Complement and Inflammation Research, Imperial College London.

More information: Aida Moreno-Moral et al, Changes in macrophage transcriptome associate with systemic sclerosis and mediateGSDMAcontribution to disease risk, *Annals of the Rheumatic Diseases* (2018). DOI: 10.1136/annrheumdis-2017-212454

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