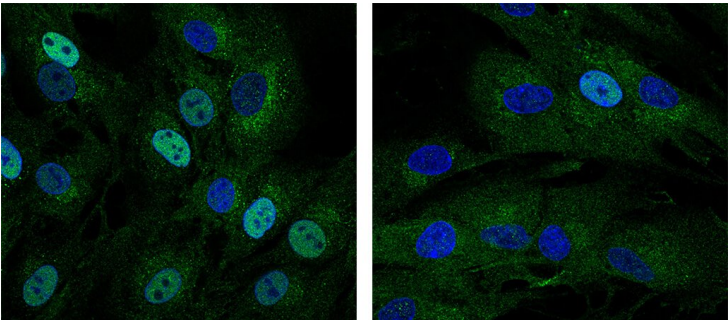


Singapore scientists discover immune pathway that causes immunodeficiency

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The novel pathway can be a target for liver disease and cancer drugs that failed trials due to inflammatory side effects



Scientists from Singapore's A*STAR's Institute of Molecular and Cell Biology (IMCB), in collaboration with doctors from KK Women's and Children's Hospital (KKH), have discovered a new immune pathway based on an investigation of severe immunodeficiency caused by a novel mutation in the NFKBIA gene. The findings were published in [The Journal of Clinical Investigation](#).

A recent investigation with a rare primary immunodeficiency disease involving a two-week old infant with recurrent infections alongside lung, skin and liver damage instigated the discovery. Scientists at A*STAR identified a new genetic variant in NFKBIA that changed the levels of soluble proteins called cytokines, produced by white blood cells to drive inflammation. Abnormally high production of one cytokine, IL-1 β , was identified as the key derangement. Crucially, the clinical team was able to suppress the patient's disease by rational administration of the IL-1 β -blocking drug, Anakinra, based on these scientific results.

The research team, along with Singapore Immunology Network (SIgN) discovered a previously unknown pathway, which controls IL-1 β production. By replicating the mutation in pre-clinical and cellular models, experimental results conclusively showed that the patient's genetic variant was the cause of IL-1 β hyper-production, and hence the disease. These findings have implications for the development of treatments against liver disease and cancer that target this novel pathway.

"While other mutations in NFKBIA have been reported before to cause disease, this mutation has never before been identified. It is the only mutation in which hyper-production of IL-1 β , severe liver cholestasis and systemic inflammation were documented. The research team believes the mutation limits immune responses via the suppression of many pro-inflammatory cytokines. Yet at the same time, it causes over-production of IL-1 β , leading to liver damage and inflammation. Using this bedside-to-bench approach of identifying the underlying genetic causes of immunodeficiency diseases, previously unknown pathways which control immune responses can be revealed. These then serve as targets for personalised treatment strategies," said Dr John Connolly, a Research Director at IMCB and co-corresponding author of the study.

The research team will further examine which new mediators are responsible for controlling IL-1 β production by this genetic variant, given that this regulatory association between the protein encoded in NFKBIA and IL-1 β was not observed previously. As this novel pathway has also been a popular target for cancer drugs that failed trials due to inflammatory side effects, the team will investigate whether these new mediators are responsible for the failure of these drugs, and determine if the side effects can be circumvented.

Image Caption: *Staining for the signalling protein NF κ B (green) in skin cells from a healthy individual (left) and the patient (right) after immune stimulation. The patient's novel NFKBIA variant impairs entry of NF κ B into nucleus (blue). This defect led to changes in cytokine production, resulting in both immunodeficiency and multi-organ damage.*