News Release

Title

Autoinflammatory keratinization disease with hepatitis/autism reveals roles for JAK1 hyperactivity

Key Points

• Clinical observations reinforced by the analysis of a knock-in mouse model confirm the crucial role of JAK1 in regulating physiological inflammatory processes.

• A novel *JAK1* mutation H596D causes autoinflammatory keratinization disease (AiKD), liver dysfunction and autism.

• The present findings expand the phenotypic spectrum that results from JAK1 hyperactivity and further underscore how gain-of-function *JAK1* mutations contribute to multisystem autoinflammation.

Summary

Heterozygous mutations in *JAK1* which result in JAK-STAT hyperactivity have been implicated in an autosomal dominant disorder that features multi-organ immune dysregulation. We identified a previously unreported heterozygous missense *JAK1* mutation, H596D, in an individual with a unique autoinflammatory keratinization disease associated with early-onset liver dysfunction and autism. Using CRISPR-Cas9 gene targeting, we generated knock-in mice with the *Jak1* missense mutation (*Jak1*KI mice) that recapitulated key aspects of the human phenotype. RNA sequencing of samples isolated from the *Jak1*KI mice revealed the upregulation of genes associated with the hyperactivation of tyrosine kinases and NF-κB signaling. Interestingly, there was a strong correlation between genes downregulated in *Jak1*KI mice and those downregulated in the brain of model mice with 22q11.2 deletion syndrome that showed cognitive and behavioral deficits, such as autism spectrum disorders. Our findings expand the phenotypic spectrum of *JAK1*-associated diseases and underscore how JAK1 dysfunction contributes to this autoinflammatory disorder.

Research Background

The Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway plays an integral role in the regulation of inflammatory processes by relaying responses between surface receptors and cytokines such as interferons and interleukins. The binding of ligands to their cognate receptors leads to the activation of JAKs, which subsequently phosphorylate associated receptors. This interaction activates STAT proteins, which can trigger downstream signaling axes or can function as transcription factors themselves. Recently, heterozygous mutations in *JAK1*, which cause that result in JAK-STAT hyperactivity, have been implicated in an autosomal dominant disorder that features multi-organ immune

dysregulation.

Research Results

We identified a previously unreported heterozygous missense *JAK1* mutation, H596D, in an individual with a unique autoinflammatory keratinization disease associated with early-onset liver dysfunction and autism. Strong nuclear staining of STAT family members were observed in the epidermis of the autoinflammatory keratinization disease patient with the *JAK1* mutation. Using CRISPR-Cas9 gene targeting, we generated knock-in mice with the *Jak1* missense mutation (*Jak1*KI mice) that recapitulated key aspects of the human phenotype. RNA sequencing of samples isolated from the *Jak1*KI mice revealed the upregulation of genes associated with the hyperactivation of tyrosine kinases and NF-κB signaling. Interestingly, there was a strong correlation between genes downregulated in *Jak1*KI mice and those downregulated in the brain of model mice with 22q11.2 deletion syndrome that showed cognitive and behavioral deficits, such as autism spectrum disorders.

Research Summary and Future Perspective

In this study, we identified a previously unreported heterozygous missense mutation in *JAK1* in an individual with inflammatory skin changes of a unique autoinflammatory keratinization disease associated with early-onset liver dysfunction and autism. Based on supporting analyses using patient samples and a knock-in mouse model generated by CRISPR-Cas9 editing, we presented evidence that activating mutations in *JAK1* are responsible for this systemic autoinflammatory phenotype. Our findings expand the phenotypic spectrum of *JAK1*-associated diseases and underscore how JAK1 dysfunction contributes to this autoinflammatory disorder.

Publication

Takuya Takeichi, John Y. W. Lee, Yusuke Okuno, Yuki Miyasaka, Yuya Murase, Takenori Yoshikawa, Kana Tanahashi, Emi Nishida, Tatsuya Okamoto, Komei Ito, Yoshinao Muro, Kazumitsu Sugiura, Tamio Ohno, John A. McGrath, Masashi Akiyama. Autoinflammatory keratinization disease with hepatitis and autism reveals roles for JAK1 kinase hyperactivity in autoinflammation. *Frontiers in Immunology*, Published online before print January 3, 2022.
DOI : https://doi.org/10.3389/fimmu.2021.737747

Japanese ver.
https://www.med.nagoya-u.ac.jp/medical_J/research/pdf/Fro_in_Imm_20220103.pdf