A systems genomics approach identifies SIGLEC15 as a susceptibility factor in recurrent vulvovaginal candidiasis.

Jaeger M, Pinelli M, Borghi M, Constantini C, Dindo M, van Emst L, Puccetti M, Pariano M, Ricaño-Ponce I, Büll C, Gresnigt MS, Wang X, Gutierrez Achury J, Jacobs CWM, Xu N, Oosting M, Arts P, Joosten LAB, van de Veerdonk FL, Veltman JA, Ten Oever J, Kullberg BJ, Feng M, Adema GJ, Wijmenga C, Kumar V, Sobel J, Gilissen C, Romani L, Netea MG (2019) A systems genomics approach identifies SIGLEC15 as a susceptibility factor in recurrent vulvovaginal candidiasis. *Sci Transl Med* 11(496), eaar3558.

Abstract

Candida vaginitis is a frequent clinical diagnosis with up to 8% of women experiencing recurrent vulvovaginal candidiasis (RVVC) globally. RVVC is characterized by at least three episodes per year. Most patients with RVVC lack known risk factors, suggesting a role for genetic risk factors in this condition. Through integration of genomic approaches and immunological studies in two independent cohorts of patients with RVVC and healthy individuals, we identified genes and cellular processes that contribute to the pathogenesis of RVVC, including cellular morphogenesis and metabolism, and cellular adhesion. We further identified SIGLEC15, a lectin expressed by various immune cells that binds sialic acid-containing structures, as a candidate gene involved in RVVC susceptibility. Candida stimulation induced SIGLEC15 expression in human peripheral

blood mononuclear cells (PBMCs) and a polymorphism in the SIGLEC15 gene that was associated with RVVC in the patient cohorts led to an altered cytokine profile after PBMC stimulation. The same polymorphism led to an increase in IL1B and NLRP3 expression after Candida stimulation in HeLa cells in vitro. Last, Siglec15 expression was induced by Candida at the vaginal surface of mice, where in vivo silencing of Siglec15 led to an increase in the fungal burden. Siglec15 silencing was additionally accompanied by an increase in polymorphonuclear leukocytes during the course of infection. Identification of these pathways and cellular processes contributes to a better understanding of RVVC and may open new therapeutic avenues.

Involved units

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Mark Gresnigt

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Interactions with immune cells (MPM)

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