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The impact of the interaction of the receptors of the Dectin-1 gene cluster in fungal and bacterial infections

The Dectin-1 cluster forms part of the group V C-type lectin-like receptors that have a single CTLD connected to an intracellular signaling domain via a stalk and transmembrane region and were thought to have arisen through gene duplication. Two of these receptors, Dectin-1 and LOX-1, have been identified as pattern recognition receptors (PRRs). Dectin-1 recognizes β-glucans, a carbohydrate present in cell walls of many fungal species, and is required for immunity to several pathogens including species of *Candida*, *Aspergillus* and *Pneumocystis*. Lox-1 has been described to bind to *Staphylococcus aureus* and *E. coli.* However, for most of the receptors of this cluster some endogenous ligands have been identified but a comprehensive analysis of their ability to function as PRRs has not been performed. Functions of receptors within the Dectin-1 cluster are predetermined, in that signaling motif(s) present within their intracellular domain dictate how they respond to extracellular stimuli. The activatory receptors Dectin-1, CLEC-2 and CLEC-9A containing ITAM-like and the inhibitory receptors MICL and MAH are containing canonical ITIM motifs. The C-type lectin-like scavenger receptor LOX-1 is containing a DDL motif and CLEC-1 is containing an uncharacterized tyrosine-based motif. Functions of ITAM bearing receptors which often are dependent on the recruitment of SYK can be counteracted by the action of ITIM bearing receptors. In this case upon co-aggregation with activating receptors, associates kinases phosphorylate the ITIM motif, which can inhibit the activation by the recruitment of the inhibitory tyrosin-phosphatases SHP1/2 or SHIP1/2. The receptors of the Dectin-1 cluster are primarily expressed on myeloid cells such as DCs, macrophages and neutrophils orchestrating a variety of cellular functions, including endocytosis, phagocytosis, cytokine production, apoptosis, activation of NFκB and production of reactive oxygen species. For the transcriptional regulation of the receptors of the Dectin-1 cluster as a paralogous gene cluster it is likely that the timing of activation and the order of receptor expression might reflect the genes' positions within their cluster. However, a comprehensive analysis of gene expression pattern of the receptors of the Dectin-1 cluster and their implication of their function in orchestrating immune responses to microbial associated molecular pattern has not been performed so far.

We hypothesized that the interaction of the ITIM or ITAM bearing receptors of the Dectin-1 gene cluster are fine-tuning pathogen-dependent immune responses in particular of Dectin-1 and LOX-1. In addition LOX-1 one might be an important and so far under recognized receptor for the detection of bacterial and maybe also for fungal pathogens.

In the proposed study the following aims will be addressed:

1. Analysis of the quantitative expression profiles of the receptors of the dectin-1 cluster on human innate immune cells (granulocytes, monocytes, macrophages, NK cells) and pulmonary epithelial cells
2. Generation of cells that differentially are expressing receptors of the Dectin-1 cluster by using the CRISPR/Cas-System (Clustered Regularly Interspaced Short Palindromic Repeats) and subsequent functional analysis of the receptor interactions

Publications

Goyal S, Castrillón-Betancur JC, Klaile E, Slevogt H (2018) The Interaction of Human Pathogenic Fungi With C-Type Lectin Receptors. *Front Immunol* 9, 1261. Details PubMed

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