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Galectin-3 recognizes fungal non-β galactoside polysaccharides and plays a role in innate host response against fungal infection

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Invasive fungal infections are one of the most important causes of infectious mortality and are responsible for 1.5 million deaths per year. Despite this fact, fungal pulmonary infections remain under-studied with few anti-fungal drugs. Majority of the invasive infections are caused by opportunistic mycoses, such as *Aspergillus fumigatus*, and the current increase in the incidence is due to escalations in infections associated with invasive interventions for cancer treatment or organ transplantation. In healthy individuals, inhaled fungi are removed by mucociliary clearance and neutralized by phagocytes in the lungs, following recognition of fungal polysaccharides by pattern recognition receptors. Especially, recognition of β-glucan by dectin-1 is critical for the induction of anti-fungal defense. β-Glucan, however, is largely buried within the glycocalyx and is masked by outer cell wall polysaccharides. It has therefore been hypothesized that immune recognition of outer polysaccharides by other host lectins precedes, and facilitates the recognition of β-glucan. We recently found that pulmonary infection with A. fumigatus rapidly induces massive accumulation of a host lectin, galectin-3, at the site of infection. Galectin-3 has been previously characterized as a soluble mammalian β-galactoside binding lectin. Interestingly, this β-galactoside binding lectin recognizes A. fumigatus-unique galactosaminogalactan (GAG), which conceals β-glucans on the fungal surface, despite the fact that GAG does not contain any β-galactosides, but rather a polymer of α-galactose and α-(N-acetyl)galactosamine moieties. Galectin-3 deficient mice displayed increased susceptibility to the infection than wild type. Collectively, these data suggest that endogeneous galectin-3 plays a critical role as a non-canonical PRR and mediates protective immune responses.

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Defects in GlcNAc-1-phosphotransferase cause bone loss, dental abnormalities and B-cell functions

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GlcNAc-1-phosphotransferase (PT) modifies newly synthesized lysosomal enzymes with mannose 6-phosphate (M6P) recognition markers which are required for their efficient targeting to lysosomes. The lack of PT activity lead to mucolipidosis II (MLII) characterized by missorting of multiple lysosomal hydrolases and the accumulation of non-degraded material in lysosomes. To investigate pathomechanisms underlying MLII, we generated a knock-in mouse that mimics clinical (e.g., reduced body length, severe skeletal abnormalities with shortened bones, spine deformity and facial dysmorphism) and biochemical symptoms of MLII patients. The progressive bone loss in MLII was demonstrated to be due to the presence of dysfunctional bone-forming osteoblasts combined with excessive osteoclastogenesis. Although the lysosomal enzymes cathepsin K and the acid phosphatase Acp5 which comprise essential components of bone-resorbing osteoclasts are hyper secreted, MLII osteoclasts are not functionally impaired. Correlative light and electron microscopy suggested that M6P-lacking cathepsin K was secreted basolaterally rather than into the resorption lacuna. Analysis of postnatal tooth development by micro-computed tomography imaging and histology revealed normal dentin and enamel formation and increased cementum thickness accompanied with accumulation of storage material in cementoblasts of MLII mice. Moreover, we observed variable targeting efficiencies of lysosomal enzymes in cells of the immune system in MLII mice which impaired in particular antigen fragmentation and presentation in B-cells maturation and the subsequent immune status whereas T-cells and dendritic cells maintained almost normal functions. Together, the inability to form Man6P residues results in lysosomal dysfunction, accumulation of variable storage material and impaired lysosomal-targeting in an enzyme and cell-dependent manner.

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