

A β -GLUCAN RESPONSE PATHWAY IN BRAIN MICROGLIA

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Beta-glucans, particularly $\beta(1\rightarrow3)$ and $\beta(1\rightarrow6)$, are carbohydrate polymers with potent immunomodulatory properties. Fungal and yeast cell walls as well as certain types of grains, such as Barley and Oat, are particularly enriched in β -glucans. Given that these sugars activate various immune cell types, they may be of value in strengthening host defenses against pathogens as well as in cancer prevention. Indeed, fungal β -glucans have been used for tumor immunotherapy in Japan for many years now. However, very little is known about the molecular and biochemical basis for the immune activation effects of these polysaccharides.

Microglia are resident immune cells in the brain that are derived from the monocytic cell lineage and closely resemble macrophages in both morphology and function. These cells play a critical role in surveillance of the CNS microenvironment, and normally dormant microglia become activated in response to various types of stress inducers, such as pathogens, ischemia, and local tissue damage. When activated, microglia give rise to local inflammation by producing reactive oxygen species as well as proinflammatory cytokines. However, activation of microglia is a double-edged sword. While microglial activity is critical for host defense, tissue repair, and tumor surveillance in the brain, the inflammation response is also thought to play a role in the pathogenesis of various neurodegenerative diseases. Therefore, a better understanding of receptors and cellular pathways that regulate microglial activity is necessary in order to identify therapeutic targets for inhibition as well as activation of microglial function. Although microglia are known to be activated by β -glucans, this activation is thought to be mediated by Toll-like receptors and little is known about the intracellular signaling pathways involved. Recent studies indicated that β -glucan recognition in dendritic cells and macrophages also involves Dectin-1, a receptor with an extracellular C-type lectin like domain fold and a cytoplasmic domain with an immunoreceptor tyrosine-based activation motif (ITAM) capable of activating intracellular signaling pathways. Therefore, we asked whether Dectin-1 may play a similar role in microglia. Here, we show that Dectin-1 is indeed present in microglia and mediates activation of microglial cells in response to zymosan, a $\beta(1\rightarrow3)$ glucan-containing particle derived from *Saccharomyces cerevisiae*. We further show that Dectin-1-mediated stimulation by zymosan results in activation of a kinase cascade involving Syk and Src family of non-receptor tyrosine kinases. Interestingly, however, Syk tyrosine phosphorylation is not required for zymosan-induced cytokine secretion. Our data suggests that Toll-like receptor-2 may be sufficient for β -glucan-induced cytokine production but Dectin-1 may play a critical role in cellular adhesion and motility.