Mushroom Nutrition, Dectin-1 and Autophagy: Implications for Celiac Disease?

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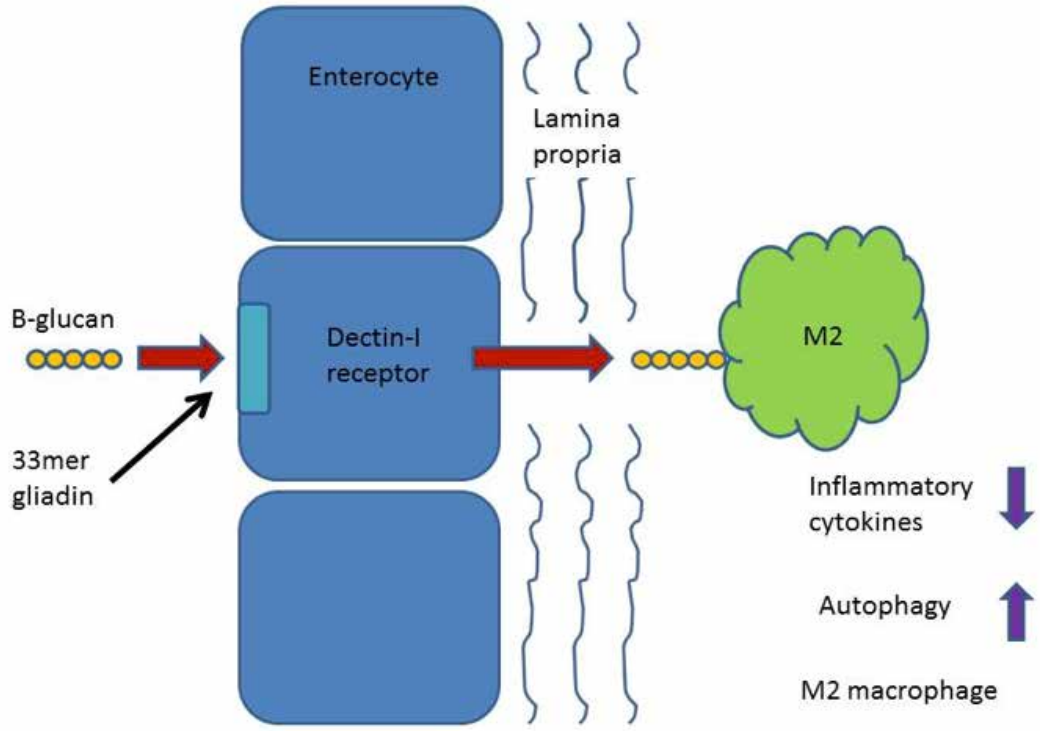
The latest studies on the aetiology of Celiac Disease (CD) provide fresh opportunities to explore the role of mushroom nutrition in the protection of the gut from the pro-inflammatory stimuli. The rationale behind this assertion is two-fold; **i)**, the Dectin-1 receptor contributes (along with changes in gut barrier function and the transferrin receptor-TfR) to the uptake of gliadin peptides by the lamina propria and **ii)**, mushroom-derived β-glucans might directly modulate macrophage activity (phenotype) by up-regulating autophagy. The assertion that mushroom polysaccharides play a role in reducing the outcome (and indeed the risk) of stress-induced inflammation might be viewed as counter-intuitive, as the majority of studies have focussed on the pro-inflammatory role of fungal-derived β-glucans. However, our suggestion is that mushroom nutrition will target enterocyte Dectin-1 receptors, decreasing the uptake of antigens; in other words mushroom-derived β-glucans will compete for binding with the 33-mer form of gliadin peptide to the Dectin-1 receptor. Further to this, recent studies have demonstrated that β-glucans, acting via the Dectin-1 receptor, up-regulate autophagy (Ohman et al., 2014). The process of autophagy is fundamental to cellular homeostasis and in particular, to maintaining the immune system in a state of tolerance. So not only is the activity of the autophagosomal-lysosomal pathway essential to maintaining the regulatory phenotype of T lymphocytes (Treg cells) (Wei et al., 2016) it is also important in maintaining macrophages in what is termed an alternatively activated form or M2 (as opposed to a pro-inflammatory M1 form).

Figure 1 – B-glucans out-compete gliadin for binding to the Dectin – I receptor



Editor´s Note: The Importance of Autophagy

Professor Yoshinori Ohsumi of Japan won the 2016 Nobel Prize in medicine for discovering the mechanisms of autophagy - how cells break down and recycle their biochemical components. Disrupted autophagy has been linked to Parkinson´s, Alzheimer´s and type-2 diabetes and cancer; disorders that appear late in life.

Autophagy controls many physiological functions where cellular components need to be degraded and recycled. It can rapidly provide energy and chemical building blocks when these are needed in response to starvation and other types of stress (ie viral infection). After infection, autophagy helps to eliminate invading germs. It contributes to embryo development and, at the other end of life, cells use autophagy to eliminate damaged components-a quality control mechanism that counteracts the negative consequences of ageing. Mutations in autophagy genes can cause genetic disease an disturbances in the autophagic manchinery have also been linked to cancer.

Reference: "Japanese scientist wins Nobel Prize in medicine for cell studies" Clive Cookson, *Financial Times*,

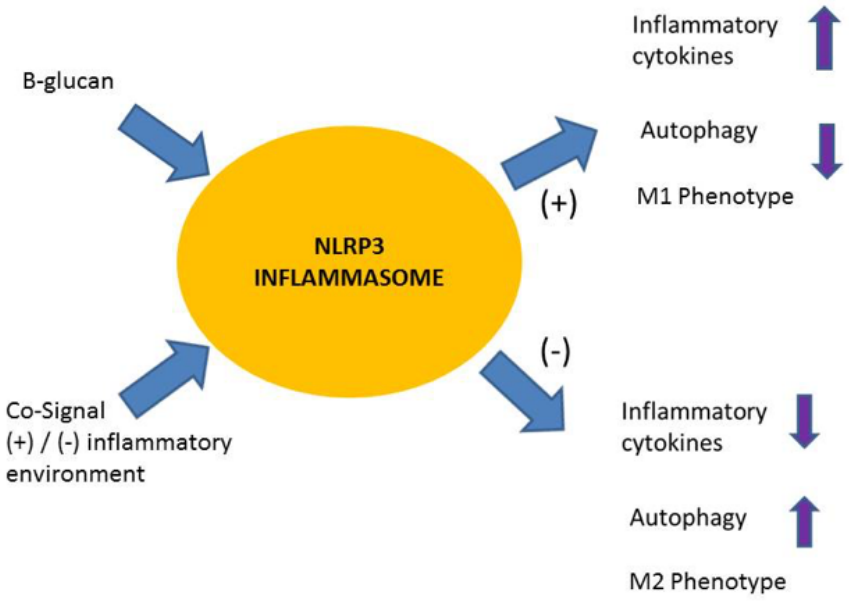


Figure 2 – The NLRP3 inflammasome drives inflammation or autophagy depending on the environment.

In a study to investigate the effect of a high fat diet (HFD) on autophagy in macrophages, Liu et al, (2015) demonstrated impaired macrophage autophagy in obese mice. They also demonstrated that knockout of essential autophagy genes enhanced systemic and liver inflammation when mice were fed a HFD in combination with lipopolysaccharide. By measuring gene and protein expression within Kupffer cells (liver macrophage-like cells) and other macrophages, they were able to demonstrate that this effect was due to a change in phenotype from an M2-like, alternative activated form, to a pro-inflammatory M1 type. The apparent role of the Dectin-1 receptor in activating inflammatory pathways as well as activating autophagy (a process that is often considered as anti-inflammatory) may be explained by the observations that inflammasomes, that are activated early in the inflammatory response, also seem to be involved in autophagy. The knock-out of the NLRP6 inflammasome blocks autophagy in intestinal goblet cells (Wlodarska et al., 2014) and blockade of NLRP3 function decreases lipopolysaccharide-induced inflammatory cytokine expression and increases autophagy in macrophages (Abderrazak et al., 2015).

These findings open up the exciting possibility that mushroom-derived β-glucans might up-regulate autophagy in gut-associated macrophages and in so doing, increase tolerance to food derived antigens such as gliadin. So not only might mushroom nutrition reduce the likelihood of developing Celiac disease in genetically susceptible individuals, it may be helpful as nutritional support during the early stages of a gluten free diet.

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