Biobran (MGN-3) acts through Toll-Like Receptor-4 (TRL-4) and Reverses the Detrimental Effects of Hyperglycaemia on Phagocytosis.

Mohammed Subhan Asif, Sally Tan, Mohamed El Mohtadi & Jason Ashworth
Centre for Bioscience, Manchester Metropolitan University, Manchester, United Kingdom.

Mohammed Subhan Asif (Mohammed.S.Asif@stu.mmu.ac.uk)
Jason Ashworth (J.Ashworth@mmu.ac.uk)

Diabetes Mellitus (DM) is a chronic condition caused by hyperglycaemia. DM has been linked to defective immune responses and increased infection risk. Innovative medicines that boost the body's innate immune system is an alternate or complementary approach to using antibiotics for treating infections. Dietary fibres such as Biobran (MGN-3) have been shown to modulate inflammation and immune responses. The aim of this study was to determine the effect of MGN-3 on the phagocytosis of Methicillin resistant *Staphylococcus aureus* (MRSA) by U937 macrophages under hyperglycaemic circumstances. Host-pathogen investigations (n=12) were performed under *in vitro* culturing conditions of increasing glucose concentration (11, 15, 20, 30mM) using U937-derived macrophages and Methicillin resistant *Staphylococcus aureus* (MRSA).

The study showed that MGN-3 treated macrophages were significantly more effective ($P<0.05$) at clearing MRSA than untreated macrophages and that phagocytosis increased with increasing MGN-3 concentration (0.5, 1.0 and 2.0 mg/ml) in a dose-dependent manner. Moreover, MGN-3 significantly reversed ($P<0.05$) the detrimental dose-responsive effects of elevated glucose on macrophage-mediated phagocytosis. It is known that bacterial lipopolysaccharide (LPS) binds to the pattern recognition receptor CD14 on the cell surface of macrophages and activates toll-like receptor-4 (TLR-4) to stimulate phagocytosis, suggesting structural similarity between LPS and MGN-3 may account for the enhanced bacterial clearance of non-endotoxin producing MRSA observed following MGN-3 supplementation. Blocking TLR-4 significantly ($P<0.05$) reversed the beneficial effects of MGN-3 on MRSA clearance, confirming MGN-3 acts at least in part through activation of TLR-4 in U937-derived macrophages.

In conclusion, MGN-3 appears to counteract the negative effects of hyperglycaemia on macrophage function by activating the TLR-4 pathway and reversing the inhibition of MRSA clearance caused by elevated glucose levels. These results may have significant impact for diabetic patients if MGN-3 can be developed as a therapy to promote bacterial clearance in diabetic patients with infected wounds.