



Mannose Treatment: A Promising Novel Strategy to Suppress Inflammation

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High glucose and fructose intake have been proven to display pro-inflammatory roles during the progression of inflammatory diseases. However, mannose has been shown to be a special type of hexose that has immune regulatory functions. In this review, we trace the discovery process of the regulatory functions of mannose and summarize some past and recent studies showing the therapeutic functions of mannose in inflammatory diseases. We conclude that treatment with mannose can suppress inflammation by inducing regulatory T cells, suppressing effector T cells and inflammatory macrophages, and increasing anti-inflammatory gut microbiome. By summarizing all the important findings, we highlight that mannose treatment is a safe and promising novel strategy to suppress inflammatory diseases, including autoimmune disease and allergic disease.

Keywords: mannose, inflammation, hexose, inflammatory diseases, mannose treatment

INTRODUCTION

Sugar intake, mainly glucose and fructose, within generic diets has increased dramatically during the past century. Hexose, especially glucose, is the most important energy source in living organisms. However, it has been well documented that consuming too much sugar can raise the incidence of many health problems, including diabetes and obesity. Recently, more studies have demonstrated the harmful effects of sugar. For example, one study reported that glucose-fructose syrup (HFCS) enhances intestinal tumor growth in mice *via* activation of glycolysis and increased synthesis of fatty acids in tumor cells that support tumor growth (1); Another study found that high fructose intake is associated with increased hepatic fatty acid synthesis and marked insulin resistance (2), and a final study showed that dietary fructose feeds hepatic lipogenesis *via* microbiota-derived acetate (3). More than that, one clinical study among US adults found that consumption of sugar-sweetened beverages (SSBs) is positively associated with total mortality (4).

In addition, high glucose intake and high fructose intake have also been proven to have pro-inflammatory roles for inflammatory diseases. Zhang et al. revealed that high glucose intake exacerbates autoimmunity in mouse models of colitis and experimental autoimmune encephalomyelitis (EAE) by promoting T helper-17 (Th17) cell differentiation (5). Jones et al. found that fructose reprograms glutamine-dependent oxidative metabolism in mononuclear phagocytes to support LPS-induced inflammation (6). Another study found that high-fructose diet (HFrD) elicited endotoxemia, could activate toll-like receptor (TLR) signaling in liver

macrophages, and induce liver inflammation (7). Another two studies also reported that dietary simple sugars alter microbial ecology in the gut and promote colitis and EAE in mice (8, 9).

Surprisingly, not all hexoses are pathogenic or pro-inflammatory. During the past few years, the immune regulatory functions of mannose, a C-2 epimer of glucose, have been revealed (10). Although mannose has been shown to be effective in the treatment of bacterial urinary tract infections by blocking the adhesion of enteric bacteria to uroepithelial cells (11–14), it was thought for a long time that the key function of mannose was to glycosylate certain proteins (15, 16), and that a mannose supplement must be given to the individuals with congenital disorders of glycosylation type Ib to support their survival (17, 18). Recently, quite a few studies have highlighted the fact that mannose is an effective suppressor of inflammation and autoimmunity (10, 19–21). Mannose has been shown to suppress numerous inflammatory diseases, including Type I diabetes (T1D) (10), asthma (10), colitis (19), obesity (20), osteoarthritis (22), chronic graft-versus-host disease (cGVHD) and lupus (21). In this review, we summarize the mechanisms of immunomodulatory effects mediated by mannose treatment, highlight mannose treatment as a promising strategy to suppress inflammation, and point to the remaining key questions that need to be addressed urgently in further studies.

REGULATORY FUNCTIONS OF MANNOSE IN INFLAMMATION

Mannose Induces Regulatory T Cells and Suppresses Effector T Cells

CD4⁺CD25⁺Foxp3⁺ regulatory T cells (Treg cells) are the most important cell population to maintain tolerance to self-antigens (23) and harmless antigens (24) (e.g. pollen) by suppressing responses of effector T cells (Teff cells) and other immune cell responses (25–28). Interestingly, Zhang et al. reported that supraphysiological levels of mannose supplemented orally through drinking water could induce Treg cells and suppress Type I diabetes and OVA-induced airway inflammation in mouse models (10). They found that mannose induced Treg cells both *in vivo* and *in vitro* through the activation of transforming growth factor beta (TGF- β) from its latent form, and they further found that the activation of TGF- β induced by mannose was mediated by increased reactive oxygen species (ROS) and integrin $\alpha_v\beta_8$. Interestingly, the increased ROS production induced by mannose was from fatty acid oxidation (FAO), as mannose treatment increased FAO, but suppressed aerobic glycolysis in CD4⁺ T cells. Moreover, mannose could also suppress type 1 helper T cells (Th1 cells) and type 2 helper T cells (Th2 cells) in a Treg cell and TGF- β independent mechanism, as they found that mannose could suppress Th1 cell cytokines (*Ifng* and *Il2*) and Th2 cell cytokines (*Il4* and *Il13*) during CD4⁺ T cell activation (before the generation of Treg cells), and they also showed that Treg cell depletion *in vivo* did not increase Th1 cell frequency in NOD mice treated with mannose (10). Overall, this encompassing work revealed the immune regulatory functions of mannose by inducing Treg cells and suppressing Teff cells, and

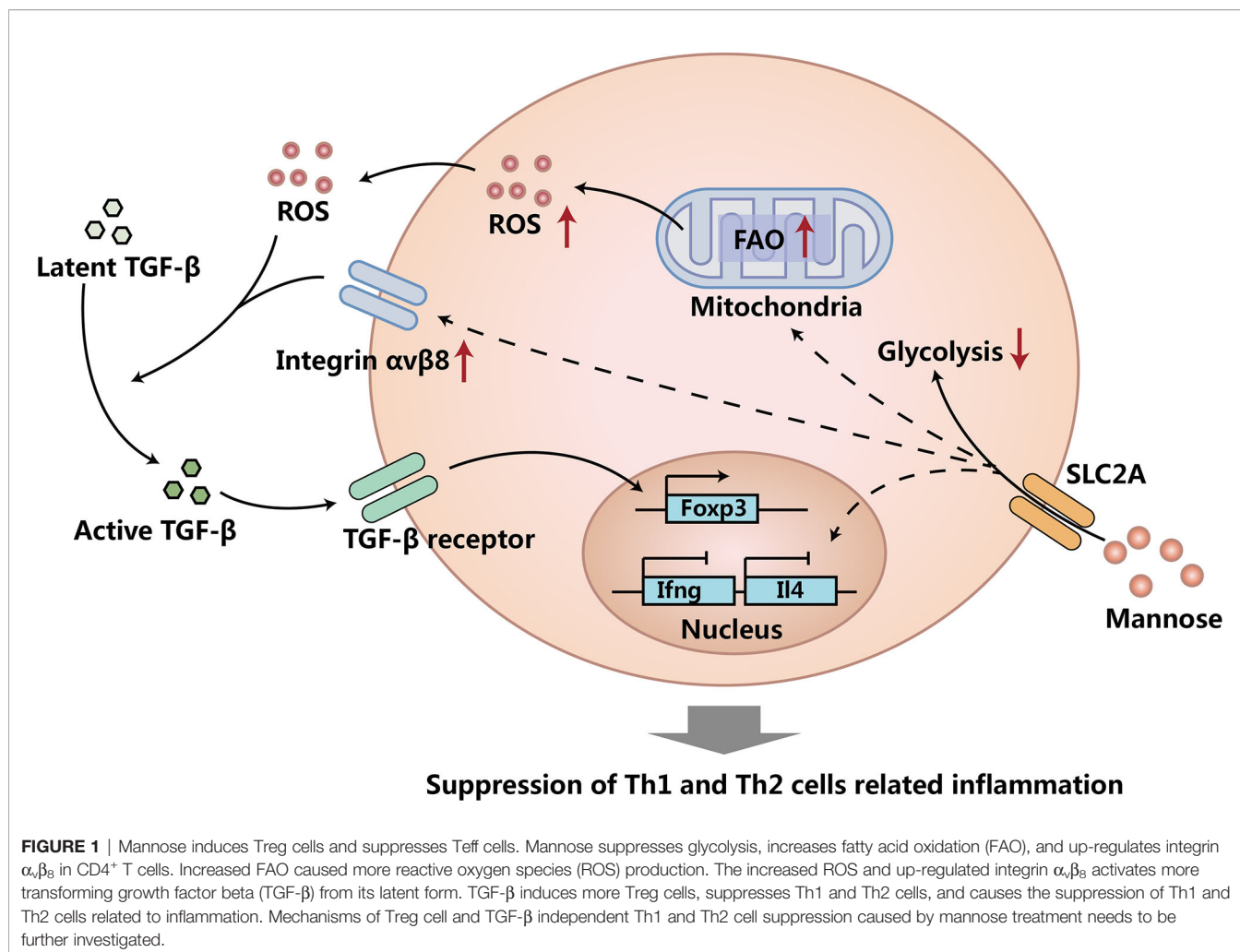
provided a fascinating new insight into the beneficial effects of this unique sugar (**Figure 1**) (10). These findings suggested that mannose could be a safe dietary supplement to promote immune tolerance and to treat/prevent human diseases associated with autoimmunity and allergy (29). In the meantime, mannose treatment did not affect *Il17* expression, suggesting that mannose may specifically induce Treg cells without affecting other protective responses such as Th17 cell-mediated gut integrity (30).

Although the clear mechanism of mannose induced Th1 and Th2 cell suppression is still unknown, it is very likely that the possible mechanism of the Treg cell and TGF- β independent suppression of Th1 cells and Th2 cells might be through the suppression of aerobic glycolysis in CD4⁺ T cells, as it has been well-proven that both differentiations and functions of Th1 cells and Th2 cells largely rely on aerobic glycolysis (31, 32). Besides suppressing Th1 and Th2 cells *via* a TGF- β activation independent mechanism, mannose might also have other mechanisms to promote Treg cell generation. One study reported that mannose treated mesenchymal stem cells (MSCs) could induce more Treg cells *via* the suppression of Interleukin 6 (IL-6) produced by MSCs (33). All these findings show that mannose can suppress inflammation *via* induction of Treg cells and suppression of Teff cells.

Mannose Suppresses Macrophage-Mediated Inflammation

Macrophages are a critical immune cell population that are important for innate immunity (34). Besides suppressing Th1 cells and Th2 cells, mannose has also been found to suppress inflammatory macrophages (19). First of all, Torretta et al. proved that mannose could limit the production of Interleukin 1 β (IL-1 β) and suppress the activation of lipopolysaccharide (LPS)-induced macrophages *in vitro*. On the other hand, mannose could also promote the survival of LPS-treated mice *in vivo*. Next, they found that mannose suppressed macrophage-derived IL-1 β production by reducing glycolysis, tricarboxylic acid (TCA) cycle, and suppressing succinate-mediated HIF-1 α activation in macrophages. Since mannose cannot be used for glycolysis efficiently, these findings further showed that mannose reduced glycolysis by competing glucose transporter (SLC2A, also called GLUT) and hexokinase (HK) with glucose, and the reduced glycolysis caused the reduction of TCA cycle. Moreover, they also demonstrated that mannose could suppress dextran sulfate sodium (DSS) induced colitis in mice *via* limiting glycolysis, TCA cycle, and IL-1 β production in macrophages. Taken together, this fantastic work revealed the immune regulatory function of mannose by suppressing IL-1 β production of inflammatory macrophages (**Figure 2**) (19).

Interestingly, the suppression of macrophage IL-1 β production completely relies on the low expression of phosphomannose isomerase (MPI) in macrophages, as overexpression of MPI in macrophages can overcome the suppression function of mannose (19). Since MPI could convert mannose-6-phosphate to fructose-6-phosphate and then use fructose-6-phosphate for glycolysis (34), these findings suggest that mannose can suppress glycolysis in cells expressing low amounts of MPI by competing hexokinase (HK)



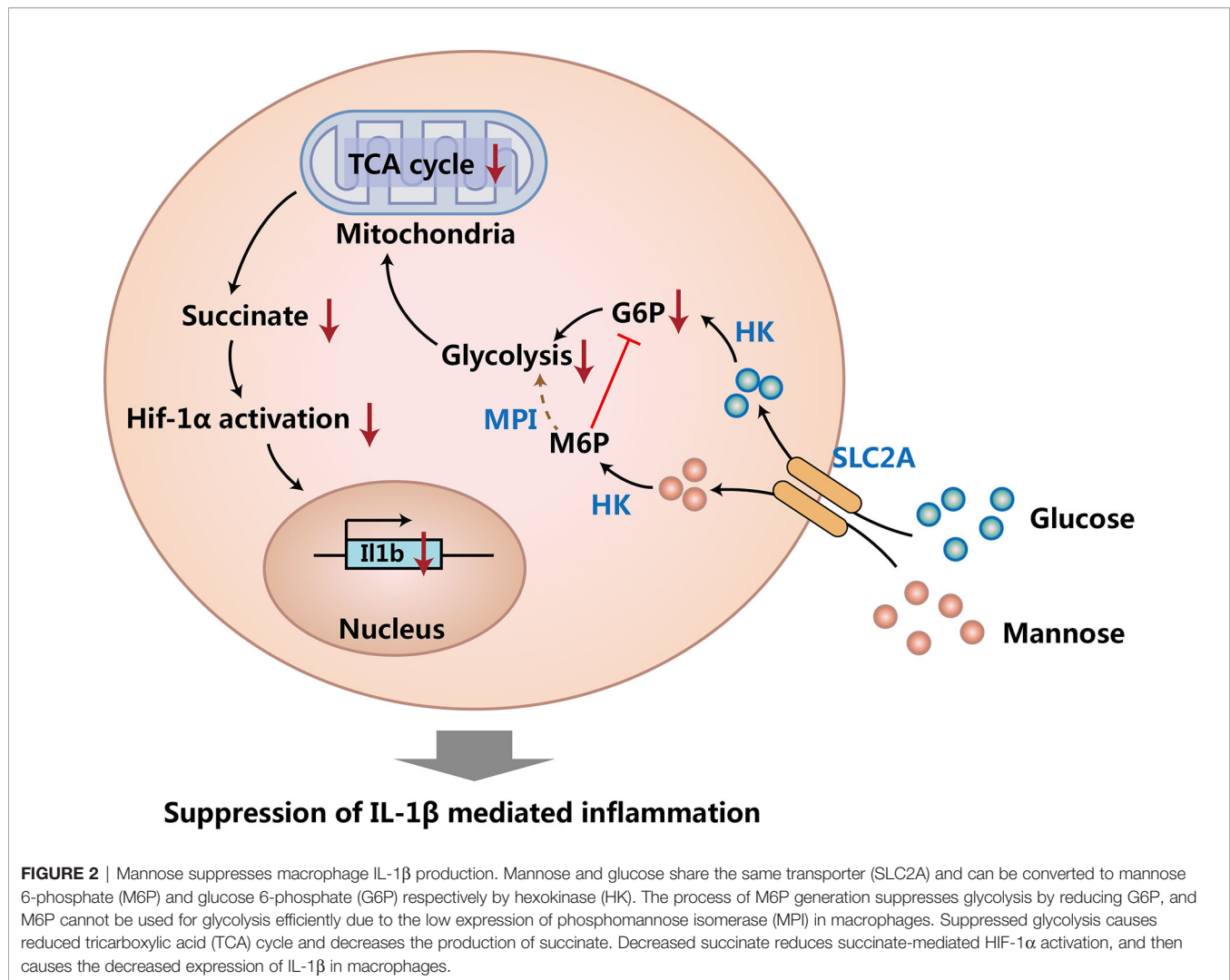
with glucose; whereas in cells expressing high amounts of MPI, mannose-6-phosphate could be converted to fructose-6-phosphate efficiently by MPI, therefore mannose could support glycolysis quite efficiently in these cells. Since it was found that mannose could suppress glycolysis in CD4⁺ T cells (10), we can presume that the expression of MPI in CD4⁺ T cells should also be quite low. Besides suppressing macrophage IL-1 β production, one study found that mannose treatment promoted proliferation, enhanced autophagy, and reduced apoptosis of IL-1 β -treated rat chondrocytes, and therefore suppressed the progression of osteoarthritis (OA) (22). All of these findings show that mannose not only suppresses IL-1 β production of macrophages, but also protects bodies from IL-1 β induced degeneration.

Mannose May Increase Anti-Inflammatory Gut Microbiome

Within the past decade, the gut microbiome has been proven to have critical functions in immune homeostasis and inflammation (35, 36). Sharma et al. showed that mannose treatment by drinking-water supplementation prevented weight gain, lowered adiposity, reduced liver steatosis, and improved glucose tolerance

during the induction of obesity in high-fat diet (HFD) mice (20). Interestingly, these beneficial effects of mannose were observed only when initiated early in life, but not when provided later. These changes in HFD mice with different ages, coupled with the fact that continuous mannose supplementation is required, made authors postulate that mannose treatment might change gut microbiome in HFD mice. Indeed, they proved that mannose treatment initiated early in life increased the *Bacteroidetes* to *Firmicutes* ratio in the gut microbiota of HFD mice, showing an association between gut microbiota composition and the timing of mannose introduction (20). The decrease of the *Bacteroidetes* to *Firmicutes* ratio in the gut microbiota has been shown to cause obesity in both mice and human, and the increase of the ratio is positively associated with weight loss (37–39). These findings show that mannose suppressed obesity by increasing the *Bacteroidetes* to *Firmicutes* ratio in the gut microbiota.

Importantly, *Bacteroides* are the most abundant members of *Bacteroidetes* in the intestinal tract of mammals, and the immunomodulatory activities of *Bacteroides* have been identified (40–43). Lower levels of *Bacteroides* in the gut microbiota have been shown to be associated with Inflammatory Bowel Disease (IBD)



(40), and polysaccharide A expressed by *Bacteroides* can induce Treg cell growth and suppress immunity (42). Consistent with these findings, mannose treatment increased *Bacteroidetes* and also reduced gene expression of inflammatory markers (*Tnfa* and *Ifng*) in adipocytes of HFD mice (20). Another study also reported that mannose treatment attenuated bone loss induced by senility and estrogen deficiency in mice, *via* the increase of Treg cells and *Bacteroidetes* (44). These findings suggest mannose treatment has gut microbiota-dependent anti-inflammatory effects.

However, an increase in *Bacteroides* is not necessarily always beneficial for anti-inflammation (45). For example, one comparative study reported that *Bacteroides vulgatus* (a genera of *Bacteroides*) in the outer membrane might be implicated in the pathogenesis of ulcerative colitis (46), another study found the growth inhibition of the *Bacteroides vulgatus* may repress exacerbation of intestinal inflammation (47). So mannose associated increases in *Bacteroidetes* might not necessarily be the main mechanism in which chronic inflammation is suppressed. Taken together, mannose treatment may have gut

microbiota-dependent anti-inflammatory effects, but the clear mechanisms need to be investigated further.

CONCLUSION AND FUTURE PERSPECTIVE

High sugar intake has long been shown to have pathogenic roles in a variety of diseases, including diabetes and obesity. Recently, functions of high-sugar intake in autoimmunity were also revealed (5, 8, 48). Unlike glucose and fructose, mannose is a special hexose that suppresses inflammation (10, 49). Also, the therapeutic concentration of circulating mannose can be reached in mice and humans (50, 51), and even a very low concentration of mannose supplemented in drinking water has a therapeutic function both *in vitro* and *in vivo* (10, 20). More than that, mannose treatment is supposed to be a safe treatment, as long-term mannose ingestion was well tolerated and did not show any adverse effect in mice and humans (50, 51).

On the other hand, there are still many important questions that need to be answered in the future. For example, it is necessary to calculate the ideal dose of mannose treatment for human inflammation, determine how mannose increases FAO in CD4⁺ T cells, and whether or not mannose can affect functions of CD8⁺ T cell and other immune cells. Moreover, since it was also reported that mannose treatment could enhance cancer chemokine therapy (52, 53), whether mannose mediated immune responses are involved during this process is totally unknown. Nevertheless, although there are still a number of key questions need to be figured out, the great therapeutic promise of mannose treatment has been disclosed.

In conclusion, mannose treatment is a promising novel strategy to suppress inflammatory diseases, including autoimmune disease and allergic disease. More intense study and research would greatly benefit patients with inflammatory disease.

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