Macromolecular excipients exert biological effects via their microbial fermentation absorbable products.

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Editorial

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> *My mitochondria comprise a very large proportion of me. I cannot do the calculation, but I suppose there is almost as much of them in sheer dry bulk as there is the rest of me. Looked at in this way, I could be taken for a very large, motile colony of respiring bacteria, operating a complex system of nuclei, microtubules, and neurons for the pleasure and sustenance of their families, and running, at the moment, a typewriter.*
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> **Lewis Thomas, The Lives of a Cell: Notes of a Biology Watcher**

In "The Lives of a Cell", L. Thomas restated a hitherto prosaic observation as a profound conjecture, i.e, that mitochondria - the earliest aerobic bacteria - may have "created" us as a 'symbiont utilitarian layer' for their survival. The same can be argued for the bacteria resident in the gastrointestinal system which, to put it bluntly, may have 'created' us in order to feed them. There are more bacteria in the human body (>500 species) than there are human cells. Most of these reside in the gut and the majority (> 90%) belong to two phyla, the Firmicutes (which include *Clostridium*, *Streptococcus* and *Staphylococcus*), and the Bacteroidetes (which include *Flavobacterium*). Aside from the sobering philosophical issues about 'free will' that such a scenario raises (separately from quantum mechanics), it seems logically imperative that the colonization of the human body by bacteria, or the colonization of human cells on bacteria, must be inextricably intertwined with regard to the survival of the two symbionts.

Recent and emerging research implicates the commensal micro-organisms residing in the gut, the gut microbiota, in a variety of dysfunctional biological processes, ranging from obesity to autoimmune disorders. With the advent of germ free (GF) murine models, unequivocal correlations have been found between the presence of specific species of bacteria with disease biomarkers and symptoms. The chain of causation leads to small molecules that the gut microbiota produce from (gut) non-absorbable food

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ingredients or macromolecular excipients such as fiber, gums and cellulosic derivatives. Fermentation of these macromolecular food or pharmaceutical excipient ingredients by the gut microbiota leads to the formation of short chain fatty acids (SCFA) which can be absorbed from the gut into the general circulation. It turns out that the magnitude and proportion of the three major SCFAs', i.e acetate (C2), propionate (C3) and butyrate (C4), are dependent on the type and quantity of macromolecular food or pharmaceutical ingredients ingested, on the ratio of fermentable to non-fermentable macromolecular species and on the composition of the phyla and species of gut microbes. The latter is itself influenced by the food and pharmaceutical ingredients (both absorbable and non-absorbable) ingested (as an example, antibiotics are notorious for causing intestinal de-population of commensal bacteria while probiotics and yogurt can repopulate select species). Diet has been shown to alter the human gut microbiome.

Gut microbiota SCFA products can regulate immune homeostasis. SCFA can promote T cell differentiation into effector or regulatory T cells in a cytokine dependent manner thereby regulating adaptive immunity and immune tolerance. In a GF murine model, the introduction of a specific bacterium in the gut was shown to induce autoimmune arthritis via the T-helper cell production of autoantibodies. The increased intestinal permeability caused by altered phylogenetic gut microbiota can cause metabolic endotoxemia; an increase in lipopolysaccharide (LPS) blood concentration. Endotoxemia can contribute to low-grade inflammation, insulin resistance and adipocyte hyperplasia that characterize the metabolic syndrome. SCFA act as signal transduction molecules via G-protein coupled receptors and as epigenetic regulators of gene expression by modulating histone deacetylases (HDAC). The phylogenetic composition of gut microbiota has been shown to differ between obese and lean humans with consequent differences in colonic fermentation patterns and SCFA concentration and composition that, in turn, are correlated with energy extraction and regulation. Colonic acetate has been demonstrated to cross the blood brain barrier and is associated with changes in the expression profiles of regulatory neuropeptides that favor appetite suppression.

At human equivalent dosages of the order of grams per day, HPMC was shown to significantly decrease cholesterol levels in hypercholesterolemic individuals on statin therapy and improve glucose homeostasis and leptin levels in a diet induced obesity mouse model. Hence, at a maximum reported oral concentration of 670 mg in the FDA, IID database, or ingesting capsules made from HPMC (~150 mg, twice daily), HPMC content in prophylactic medicinal products is within 1 order of magnitude of that required to alter gut microbiota composition or glucose and lipid homeostasis; its biological effect is hence significant. Studies with diet suplemented, fermentable carbohydrates (acacia gum, high amylose starch, partially hydrolyzed guar gum, pectin) in a range of 10 grams through 108 grams once daily have demonstrated biological effects ranging from a reduction of cholesterol, increasing insulin sensitivity, weight reduction and decreased cytotoxicity of the fecal aqueous phase, that were attributed to an increase in the colonic SCFA levels. There is extensive experimental and clinical trial data to suggest that dietary inulin may counteract the effects of carcinogens, via production of anti-proliferative short-chain fatty acids formed by bacterial fermentation of inulin in the gut.

Pharmaceutical dosage forms contain various macromolecular, partially or incompletely digestible excipients such as cellulose esters or ethers, starches and gums that may be fermented in the colon. When consumed orally as a prophylactic treatment, these excipients can alter colonic SCFA concentration and composition, in addition to altering the enterohepatic pools. Pharmaceutical scientists must become cognizant of the fact that the magnitude or the ratios of cellulose acetate, cellulose acetate butyrate and cellulose acetate

propionate in prophylactic sustained release dosage forms alters, not only the API release profile and ADME, but also a myriad of SCFA activated downstream effectors that are dependent on the mass and/or mass ratios of these ingredients in the formulation. Considering that SCFA is implicated in a wide spectrum of biological effects, it would be prudent to ensure that the biological effects of such macromolecular excipients do not superimpose on those of the API, and if they do, the extent of those effects is either known or can be estimated prior to beginning clinical trials.

Conventional wisdom has long held that because macromolecular excipients are not absorbed into the bloodstream, they do not exert any biological effects. But then again, for a period of time lasting for more than 2000 years, conventional wisdom accepted the Ptolemiac geocentric model of the universe as the truth. Not only do 'small molecule' pharmaceutical excipients exhibit biological activity; orally administered macromolecular excipients do so as well.