

## WHAT IS NEW? WHAT IS HOT?

# Itaconate itinerary changed: Now it's a potential metabolite to switch-off inflammation!

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### Industry interest of itaconate

Itaconic acid is well known as a precursor for polymer synthesis and has been involved in industrial processes for decades. Itaconate was first identified in 1836 as a molecular product of citric acid distillation. In 1931, it was reported that itaconate could be synthesized *in vivo* by an *Aspergillus* species (subsequently named *Aspergillus itaconcus*) isolated from dried salted plums. This has spurred the development of emerging metabolic engineering strategies and process optimization technologies to enhance itaconic acid production. Today, itaconic acid has a huge world market and feeds into the preparation of industrial polymers and bioactive compounds in the personal care, agriculture, pharmaceutical, and medicine sectors.<sup>1</sup> Research into more efficient methods of biomanufacturing itaconate is extremely active, because it represents a sustainable alternative to traditional crude oil-based polymers.<sup>2, 3</sup>

### Immunological interest of itaconate

Recent studies have unraveled a surprising transformation of itaconate from its original industrial polymer component to an important contributor to mammalian immunity and inflammation regulation.<sup>4</sup> Itaconate was initially believed to have only anti-bacterial function due to its ability to inhibit isocitrate lyase, a bacterial glyoxylate shunt enzyme, and bactericidal actions.<sup>5</sup> Although itaconate is one of the most highly induced metabolites in activated macrophages, its precise mechanism of action remains poorly understood. One of the landmark studies by Lampropoulou *et al.* (2016) has expanded the physiological roles of itaconate beyond a direct anti-bacterial action, to include regulation of TLR-mediated inflammatory cytokine production, and provided a physiological regulatory mechanism to control electron transport chain flow, succinate levels, reactive oxygen species (ROS) production, and tissue inflammation.<sup>6</sup> This study observed that pre-treatment with diethyl itaconate (DI), a membrane permeable non-ionic form of itaconate,

strongly inhibited macrophage production of several cytokines viz., IL-12, IL-6 and IL-1 $\beta$  as well as production of nitric oxide (NO) and ROS in response to a variety of inflammatory challenges. Moreover, the anti-inflammatory effects of itaconate were demonstrated in an *in vivo* animal model of cardiac ischemia reperfusion (IR) injury, wherein the intravenous infusion of DI during ischemia has been shown to markedly reduce myocardial infarct size.<sup>6</sup>

Recently, two studies published in *Nature* journal have emphasized the role of itaconate as a regulator of macrophage function and breaking signal for inflammation. Working with human cells and mouse models, Mills *et al.* (2018) found that itaconate is involved in the activation of the anti-inflammatory transcription factor nuclear factor erythroid-2-related factor 2 (NRF2) by lipopolysaccharide in mouse and human macrophages.<sup>7</sup> Mechanistically, itaconate has been shown to directly modify proteins via alkylation of multiple cysteines and a lysine residue on the NRF2 regulator protein, kelch-like ECH-associated protein1 (KEAP1). This action enables the transcription factor NRF2 to increase the expression of genes associated with anti-oxidant and anti-inflammatory effects. These results imply that itaconate is an important anti-inflammatory molecule and it acts via NRF2 to limit inflammation. This study has also described the *in vivo* use of a cell-permeable itaconate derivative (4-octyl itaconate) as a potential pre-clinical drug entity against lipopolysaccharide-induced lethality.

While the major effects of itaconate on cellular metabolism during macrophage activation have been attributed to the inhibition of succinate dehydrogenase, yet this inhibition alone is not sufficient to account for the pronounced immunoregulatory effects. In this context, the research by Bambouskova *et al.* (2018) have shown that itaconate and its derivative dimethyl itaconate induce electrophilic stress, and react with glutathione, thereby inducing both

NRF2-dependent and independent responses.<sup>8</sup> Most importantly, this study unraveled that itaconate reduces levels of a key protein - known as I $\kappa$ B-zeta (I $\kappa$ B $\zeta$ ) - in the IL-17 inflammatory pathway. Since IL-17 plays a role in many autoimmune diseases as well as metabolic disorders, a compound that puts a check on this pathway potentially could be helpful for treating many serious ailments. The mice model study by Bambouskova *et al.* (2018) suggests that itaconate compounds might be useful for treating autoimmune diseases, especially psoriasis as well as multiple sclerosis.<sup>8</sup>

### How the emerging science of itaconate is related to translational applications?

While pharmacological intervention targeting itaconate is possible in the future, one should also remember that lifestyle modifications (diet and exercise) might offer those itaconate-derived health benefits, non-pharmacologically. Recently several studies have identified therapeutically important natural compounds and molecules that have the ability to pharmacologically modulate the macrophage polarization, particularly towards the M2 phenotype.<sup>9</sup> These natural modulators include several classes of chemical entities such as stilbenes, polyphenols, flavonoids, terpenes, anthraquinones and various others from diverse origins. It would be worth and national priority research to probe whether these natural compounds could increase the endogenous itaconate levels and thereby curtail inflammation. Current evidence also emphasizes on how exercise training, more precisely the endurance exercise training, could mediate the polarization state of tissue macrophages from an M1 to an M2 anti-inflammatory phenotype.<sup>10</sup> Future studies should investigate whether these health benefits of exercise could occur through the expanding molecular actions of itaconate and its effector functions.

In nutshell, with the functional itinerary of itaconate changed to a distinct immunoregulatory and immunomodulatory role, clinically relevant studies should exploit its antioxidant and anti-inflammatory actions. Recent research brings promise and hope for the treatment of metabolic disorders and

autoimmune diseases where there is a close-association of excessive inflammation and/or oxidative stress.

### Competing interests

None declared

### Citation

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