Veras FP, Peres RS, Saraiva AL, Pinto LG, Louzada-Junior P, Cunha TM, Paschoal JA, Cunha FQ, Alves-Filho JC. (2015). Frutose 1,6-biphosphate, a high-energy intermediate of glycolysis, attenuates experimental arthritis by activating anti-inflammatory adenosinergic pathway. *Sci Rep*. 5: 15171.

Fructose 1,6-bisphosphate (FBP) is an endogenous intermediate of the glycolytic pathway. Exogenous administration of FBP has been shown to exert protective effects in a variety of ischemic injury models, which are attributed to its ability to sustain glycolysis and increase ATP production. Here, we demonstrated that a single treatment with FBP markedly attenuated arthritis, assessed by reduction of articular hyperalgesia, joint swelling, neutrophil infiltration and production of inflammatory cytokines, TNF and IL-6, while enhancing IL-10 production in two mouse models of arthritis. Our mechanistic studies showed that FBP reduces joint inflammation through the systemic generation of extracellular adenosine and subsequent activation of adenosine receptor A2a (A2aR). Moreover, we showed that FBP-induced adenosine generation requires hydrolysis of extracellular ATP through the activity of the ectonucleosides triphosphate diphosphohydrolase-1 (ENTPD1, also known as CD39) and ecto-5'-nucleotidase (E5NT, also known as CD73). In accordance, inhibition of CD39 and CD73 abolished anti-arthritic effects of FBP. Taken together, our findings provide a new insight into the molecular mechanism underlying the anti-inflammatory effect of FBP, showing that it effectively attenuates experimental arthritis by activating the anti-inflammatory adenosinergic pathway. Therefore, FBP may represent a new therapeutic strategy for treatment of rheumatoid arthritis (RA).