Abstract #: 9

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The Development of a Novel, Targeted and Less Toxic Anti-Inflammatory Drug for the Treatment of Gout.

Objectives: Gout is one of the most painful types of arthritis and its prevalence is increasing worldwide. It is characterized by acute inflammatory episodes initiated by monosodium urate crystals (MSU). The use of anti-inflammatory drugs to treat gout is challenging since most patients suffer from co-morbidities. Colchicine effectively dampens MSU-induced inflammation but is associated with undesirable side effects. Since colchicine exhibits specificity towards the molecular pathways involved in gout we modified its structure to render it less toxic. Colchicine binds to beta-tubulin isoforms with different affinities. Using a rational drug design approach, we increased the affinity of colchicine for a beta-tubulin isotype whose expression is enriched in leukocytes including neutrophils. Neutrophils play a key role in gout attacks.
Methods: We generated colchicine derivatives that preferentially bind the beta-tubulin isotype expressed in leukocytes and tested them in in vitro assays on human neutrophils, including the MSU-induced secretion of IL-8, the synthesis of IL-1, the production of reactive oxygen species and the increase in cytoplasmic calcium. Their anti-inflammatory activity was assessed in the air-pouch model of MSU-induced inflammation.
Results: One of the colchicine derivatives tested inhibits MSU-induced, neutrophil activation at a 100-fold lower dose than colchicine in all the in vitro assays. This compound also significantly inhibited leukocyte recruitment at a 10-fold lower dose than colchicine in the air pouch model. Similar observations were made for the second compound at doses 10- to 100-fold lower than colchicine.
Conclusions: We have developed anti-inflammatory compounds that may offer gout patients a safer drug as well as patients with other diseases treated with colchicine. To our knowledge, this is the first demonstration that beta-tubulin isotypes are a potential therapeutic target to treat neutrophil-driven inflammation in gout.