MBI AND DUKE-NUS JOINT SEMINAR ANNOUNCEMENT

An old drug is doing new tricks: Inter-organ communication as a therapeutic strategy against inflammation



by Jui-Hsia Weng

USAI Harvard Medical School

HOSTED BY MITHILESH MISHRA

Inflammation is a protective response to challenges including infection and tissue stresses, but failure to resolve inflammation leads to diverse diseases. Colchicine has been used as a traditional medicine for millennia. It is still widely prescribed to treat inflammatory disorders and is being actively repurposed. Colchicine binds tubulin and depolymerizes microtubules, but how this blocks myeloid cell recruitment to inflamed tissues is unknown. I found that myeloid cell activation was blocked by post-colchicine plasma, but not by colchicine itself, arguing for an indirect mechanism. Therapeutic doses of colchicine depolymerized microtubules selectively in hepatocytes and not in circulating myeloid cells. This activated Nrf2, leading to hepatocyte protection and secretion of anti-inflammatory hepatokines including GDF15, a member of the TGF-beta family. Nrf2 and GDF15 were required for anti-inflammatory action of colchicine in vivo. Post-colchicine plasma inhibited inflammatory signaling in myeloid cells in a GDF-15 dependent manner by positive regulation of SHP-1 (PTPN6) phosphatase. My work shows that the efficacy and safety of colchicine depend on its selective distribution to hepatocytes and reveals a new axis of liver-myeloid cell communication. Plasma GDF15 levels and myeloid cell SHP-1 activity may be useful pharmacodynamic biomarkers in colchicine repurposing trials.

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