A novel NOX2 inhibitor CYR5099 attenuates neutrophilic oxidative stress and inflammatory paw injury in mice

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Overwhelming activation of neutrophils has a pathogenic effect in inflammatory diseases. NADPH oxidase 2 (NOX2) is a major respiratory burst oxidase in neutrophils to generate myriad of superoxide anion and derived reactive oxygen species (ROS). NOX2 is an emerging therapeutic target for treating neutrophilic inflammatory diseases. Herein, we show that 4-[(4-(dimethylamino)butoxy)imino]-1-methyl-1H-benzo[f]indol-9(4H)-one (CYR5099) acts as a novel NOX2 inhibitor and exerts protective effect against complete Freund’s adjuvant (CFA)-induced inflammatory arthritis in vivo. CYR5099 selectively inhibited respiratory burst but not degranulation in activated human neutrophils. The upstream signaling of NOX2 was not altered by CYR5099. Significantly, CYR5099 blocked the enzymatic activity of NOX2 in activated human neutrophils as well as reconstituted subcellular assays. Using a CFA-induced inflammatory arthritis model, CYR5099 ameliorates the ROS production and paw edema in mice. Our findings suggest that CYR5099 is a novel NOX2 inhibitor and may exhibit therapeutic potential for treating neutrophil-dominant oxidative inflammatory diseases.