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Exploring the anti-inflammatory activity of the plant-derived phytochemical sulforaphane from cruciferous vegetables

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Dysregulation of immune responses results in the development of chronic inflammatory conditions. The current frontline therapy, glucocorticoids, are effective immunosuppressive drugs but come with a trade-off of cumulative, debilitating side effects with sustained use. Clearly, alternative drug options with improved safety profiles are urgently needed. Macrophage Migration Inhibitory Factor (MIF) is a pleotropic pro-inflammatory cytokine and integral component of immune and inflammatory responses. MIF counter-regulates the immunosuppressive effects of glucocorticoids and promotes NLRP3 inflammasome activation.[1, 2] Elevated MIF is a feature of multiple diseases, including multiple sclerosis, rheumatoid arthritis, and systemic lupus erythematous. Given the association of increased MIF in serum with multiple disease models, it is considered MIF may be a plausible, specific druggable target in treatment of chronic inflammatory and autoimmune diseases, particularly as a target for glucocorticoid-sparing therapy to reduce the dose or duration of glucocorticoid treatment. The organosulfur isothiocyanate phytochemical sulforaphane (SFN) is extracted from cruciferous vegetables, including broccoli and Brussel sprouts following hydrolysis of its inactive precursor, glucoraphanin. SFN has antioxidant and cancer chemoprotective properties, and promotes NRF2 antioxidant signalling to upregulate the expression of numerous antioxidant enzymes. SFN has been shown to covalently modify MIF with high reactivity and is a potent inhibitor of MIF tautomerase activity. However, to date, no such study has evaluated the role of SFN as a novel inhibitor of MIF-mediated inflammatory pathway activation. Using cell-based assays, we have sought to investigate the role of SFN as an inhibitor of multiple inflammatory pathways which have previously implicated MIF as a possible regulator. Our initial work has examined SFN as an inhibitor of NF-κB activity, inflammasome activation, and evaluated if MIF is required for this effect. RAW264.7 murine macrophage cells stably expressing NF-κB-luciferase reporter construct were pre-treated with SFN (2.5 μM) before the induction of inflammation, via LPS (100ng/mL). For NLRP3 inflammasome activation, cells were subsequently treated with the NLRP3-specific inflammasome activator, nigericin (10 μM). TNF, IFN-β and IL-1β cytokine expression was measured by ELISA and NF-κB activity by luciferase reporter assay. We found SFN is a potent inhibitor of NF-κB activity and inhibits release of the pro-inflammatory cytokine IL-1β through inhibition of NLRP3 inflammasome activation. Finally, co-incubation of SFN with the glucocorticoid dexamethasone significantly suppressed TNF and IFN-β expression, demonstrating steroid sparing activity of SFN *in vitro*. Thus, SFN may be a suitable treatment for disruption of inflammatory pathways and suggest some of these effects may be mediated through direct interactions with MIF.

Keywords: Glucocorticoids; isothiocyanate; inflammation; macrophage migration inhibitory factor (MIF)

Ethics Declaration

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References

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