A90  IMMUNOMODULATORY DRUGS CAN INHIBIT THE EXTRACELLULAR RELEASE OF HMGB1 FROM CULTURED HUMAN MONOCYTES

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Background  The endogenous, nuclear protein High Mobility Group Box chromosomal protein 1 (HMGB1) is secreted by activated macrophages/monocytes and, once extracellular, promotes inflammation. Extracellular HMGB1 is present in the synovitis of patients with rheumatoid arthritis (RA) and blockade of HMGB1 by specific antibodies ameliorates experimental arthritis. In addition, intra-articular injections of recombinant HMGB1 induce arthritis in mice. The authors hypothesise that HMGB1 represents an endogenous mediator of arthritis as well as a target molecule for successful therapeutic intervention in RA. As no HMGB1-specific therapy exists for use in humans, the authors decided to investigate whether HMGB1 secretion is inhibited by anti-rheumatic and anti-inflammatory drugs already in use in clinical practice.

Methods  Cultures of primary human monocytes were pre-incubated with cortisone, dexamethasone, gold sodium thiomalate, methotrexate, chloroquine, colchicine, pravastatin, interleukin 1 (IL1) receptor antagonist or soluble tumour necrosis factor (TNF) receptor for 1 h and then activated with lipopolysaccharide (LPS) + interferon γ (IFNg). HMGB1 and TNF secretion were determined after 24 and 9 h of stimulation in enzyme-linked immunosorbent spot assays. Cell viability was recorded by Annexin V staining. The effects of the investigated drugs were evaluated by comparing the number of spots in wells treated with a given drug with the number of spots formed by non-exposed activated cells.

Results  Addition of dexamethasone or chloroquine significantly suppressed both HMGB1 secretion and TNF secretion. In contrast, gold sodium thiomalate significantly suppressed HMGB1 secretion but did not affect TNF secretion. Cortisone, methotrexate, colchicine, pravastatin, soluble TNF receptor and IL1 receptor antagonist did not inhibit HMGB1 secretion.
Cell viability was consistently more than 90% in co-cultures with all tested drugs, with the exception of high doses of chloroquine which strongly suppressed HMGB1 release and also increased apoptosis.

**Conclusion** By this in vitro system, the authors could define clinically available anti-inflammatory drugs with HMGB1 suppressive features. The mechanisms of action for the drugs are likely to differ for the different drugs. Gold sodium thiomalate has previously been shown to retain HMGB1 intranuclearly and this study indicates that dexamethasone has a similar mode of action. Thus, our data indicate that dexamethasone, gold sodium thiomalate and chloroquine all suppress the active secretion of HMGB1 from monocytes, a mechanism that most likely contributes to the beneficial effects mediated by these compounds in patients with RA.
Immunomodulatory drugs can inhibit the extracellular release of HMGB1 from cultured human monocytes

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