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Improving Hydroxychloroquine's Efficacy for Systemic Lupus Erythematosus (Lupus) Treatment in a Preclinical Mouse Model

Rationale: Systemic lupus erythematosus is an autoimmune disease driven by antinuclear antibodies. Hydroxychloroquine (HCQ), a first-line lupus treatment for nearly 60 years, prevents flares by suppressing lupus autoimmunity while sparing normal immune function. However, its mechanism remains unclear. We hypothesize that HCQ enhances protective B cell tolerance via sphingomyelin synthase 2 (SMS2) in the germinal center (GC). SMS2 prevents lupus in mice by activating PKCÎ´-mediated apoptosis in autoreactive GC B cells. The antitumor drug 2OHOA alleviates lupus in NZBWF1 mice by activating the SMS2/PKCÎ´ pathway. Since HCQ has been linked to increased SM synthesis, we propose that HCQ may function by activating the SMS2/PKCÎ´ tolerance pathway in GC B cells.
Methods: NZBWF1 mice received HCQ (10, 13, or 16 mg/kg/day) and 2OHOA (200 or 400 mg/kg/day) via oral gavage for four weeks to determine the most effective dosage in reducing lupus markers, including serum anti-dsDNA IgGs, proteinuria, GC B cell proportion, and kidney morphology. Control mice received PBS and corn oil. The most effective HCQ and 2OHOA doses were then halved and combined in a four-week treatment to assess whether reduced dosages maintained or enhanced therapeutic effects.
Results: HCQ at 16mg/kg/day and 2OHOA at 400mg/kg/day significantly reduced lupus markers, with an even greater reduction observed in the combination treatment (HCQ 8 mg/kg/day and 2OHOA 200 mg/kg/day). In cultured B cells, HCQ increased SMS2 expression, and its effect on apoptosis was SMS2-dependent. These findings suggest that both HCQ and 2OHOA may activate SMS2/PKCÎ´ regulated tolerance in GC B cells, potentially enhancing their therapeutic effect.
Significance: Long-term HCQ accumulation can lead to adverse effects, often forcing patients to discontinue treatment and increasing the risk of lupus flares. Understanding HCQ’s mechanism of action may help develop strategies to inhibit lupus autoimmunity with reduced HCQ dosage.