

Sulphur balneotherapy and patient's immunity: H₂S effects on human CD4+ T cell polarization to Th17 and Treg phenotype

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H₂S - known for decades as a toxic gas - is endogenously generated from cysteine and belongs to the family of gasotransmitters, such as nitric oxide (NO) and carbon monoxide (CO) (Szabo C, 2007). H₂S-donors, sulfur balneotherapy and sulfur spa waters might be beneficial in the treatment of colitis, asthma, psoriasis and systemic lupus erythematosus (Fiorucci S, 2007; Zhang G, 2013; Han Y, 2013). However, the role of H₂S in inflammation is still under debate and the molecular mechanisms of H₂S in immune regulation remain largely unknown.

H₂S has been reported to exert both pro-inflammatory and anti-inflammatory effects. The inhibition of endogenous H₂S production suppresses inflammatory response (Miller et al., 2012). On the other hand, administration of exogenous H₂S has been shown to possess anti-inflammatory effects (Zanardo et al., 2006) i.e. down-regulation of pro-inflammatory cytokine expression (IL-1, TNF, IFN IL-12, IL-23) and increased expression of IL-10, a classical anti-inflammatory cytokine.

We have previously demonstrated both in vitro and in vivo on primary psoriatic lesions that hydrogen sulfide not only reduce the basal expression and secretion of IL-8, but also interfere with IL-17- and IL-22-induced IL-8 production. Moreover, we showed that hydrogen sulfide dramatically decreased CD4 T cell proliferation in response to mitogens and reduced IL-2 production (Mirandola P et al., 2007).

A fine balance between IL-17 producing CD4+ T cells (Th17) and Treg has recently emerged as a crucial point in inflammation associated with various autoimmune and immune-mediated diseases. The Th17 and Treg developmental pathways are reciprocally interconnected. Th17 cells represent a pro-inflammatory subset, that contributes to autoimmunity and tissue damage (Burkett PR, 2015). On the contrary, Treg cells have a suppressor activity important in the establishment and maintenance of self-tolerance.

Recently, H₂S has been suggested to be involved in T cells lineage polarization and T cell-associated immune homeostasis. Yang et al. demonstrated that H₂S is

required for FoxP3 stable expression and Treg differentiation in mouse models. Reduced levels of H2S were responsible for the impairment of CD4+Foxp3+ Treg cell differentiation and function and the onset of systemic autoimmune disease in mice (Yang R, 2015).

Given the pivotal role of Th17/Treg cell ratio in the onset and clinical evolution of immune-mediated pathologies, we investigated the effects of exogenous H2S on human resting CD4 T cell polarization to Th17 and/or Treg phenotype.

We differentiated ex-vivo human resting CD4+ (Th0) T cells to Th17 or Treg lineages treating cell cultures with the H2S-releasing donor NaHS. By RT-PCR, we observed that NaHS treatment increased Foxp3 mRNA levels in CD4+ T cells cultured under Treg-polarizing conditions. However, NaHS was also able to increase ROR γ T mRNA levels in CD4+ T cells under Th17 polarizing conditions, suggesting a role of sulfurs in the activation of both polarization pathways.

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