Thiols Decrease Human IL-4 Production and IL-4-Induced Immunoglobulin Synthesis

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N-acetyl-L-cysteine (NAC) is an antioxidant precursor of intracellular glutathione (GSH) [1] which is usually given in man as a mucolytic agent. Due to its ability to decrease HIV replication [2] and to restore intra- and extracellular GSH levels, NAC has been recently proposed as an anti-HIV agent [2]. In vitro, NAC and GSH have been shown to act on T cells by increasing IL-2 production, synthesis and turnover of IL-2 receptors, proliferation [3, 4], cytotoxic properties [5] and resistance to apoptosis [4]. NAC and some other thiol antioxidants have also been reported to regulate the activation of some transcription factors involved in IL-2 production, such as NF- κ B and activator protein-1 transcription factors [6]. In view of the effects of NAC on T cells, we have evaluated whether NAC could selectively regulate Th1- or Th2-derived cytokine production.

We have observed that NAC and GSH dose dependently decrease human IL-4 production by PMA plus ionomycin-stimulated peripheral blood T cells and by Con A or anti-CD3 mAb-stimulated ThO- and Th2-like T cell clones. This effect (ranging from 0.5 to 20 mM) was also associated to a decrease of IL-4 mRNA transcription. In contrast, NAC and GSH have no effect on IFN- γ production but increase IL-2 production as well as T cell proliferation. One can speculate that thiols may affect the activation of transcription factors belonging to the NF- κ B family and implicated in the transcription of IL-4 (such as NEAT) [7].

A key function of IL-4 is its ability to induce immunoglobulin (Ig)E and IgG4 production by human B cells [8].

This production requires a second primary signal given by triggering CD40 (by an anti-CD40 mAb or by CD40 ligand) [9] and is tightly controlled by the interaction of the cell surface

molecules CD21 and CD23 [10]. As we observed that NAC is able to decrease IL-4 production by T cells, we have tested whether NAC would also inhibit IL-4-induced IgE and IgG4 production by human peripheral blood mono-nuclear cells. Both NAC and GSH selectively and dose dependently decrease IL-4-induced IgE and IgG4 production by peripheral blood mononuclear cells. Interestingly, NAC and GSH also act directly on tonsillar B cells stimulated with IL-4 plus anti-CD40 mAb by decreasing the mature ϵ mRNA expression, hence decreasing IgE production. In contrast, IgA and IgM production was not affected. Finally, NAC decreased the expression of CD21 and CD40 on IL-4-stimulated tonsillar B cells while the expression of other markers such as CD11a, CD19 and CD20 was unaffected [11]. Taken together, these effects of NAC on IL-4 production, ϵ mature mRNA transcription and the expression of surface molecules involved in IgE regulation could explain the decrease of human IgE production in vitro.

Antioxidants without a thiol (SH) group (such as L-car-nitine, catalase, ascorbic acid and SOD) and the non-antiox-idant molecules, in which the SH group has been oxidized or alkylated (such as methionine, SMC and GS-SG) have no activity in the decrease of IL-4 and IgE/IgG4 production. Thus, free SH groups are critical for molecules to decrease IL-4 and IgE production [11].

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These in vitro findings were extended to an in vivo mouse model. Mice were immunized with ovalbumin to induce an IgE response and were given NAC dissolved in drinking water. One week after immunization, both ovalbu-min-specific IgE and IgG1 (the mouse isotype equivalent of human IgG4) responses were highly reduced compared to untreated mice [11].

In conclusion, these results demonstrate that NAC, GSH and other thiols may control the production of both the Th2-derived cytokine IL-4 and IL-4-induced immunoglobulins in vitro and in vivo. Experiments are in progress to define the molecular target(s) of thiols as they may constitute new molecules for the treatment of Th2-mediated diseases, such as allergic disorders and AIDS.

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