Intracellular thiols contribute to Th2 function via a positive role in IL-4 production.:

Monick MM, Samavati L, Butler NS, Mohning M, Powers LS, Yarovinsky T, Spitz DR, Hunninghake GW

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Augmenting intracellular soluble thiol pools (approximately 2-fold) with 15 mM NAC blocked induction of IFN-gamma and increased production of IL-4 without causing significant changes in intracellular glutathione levels.

A number of lung diseases, including many interstitial lung diseases and HIV infection, are associated with decreases in intracellular thiols. Altered Th1/Th2 T cell balance has also been associated with disease progression in many of the same diseases. IFN-gamma and IL-4 are critical effector cytokines of Th1 and Th2 cells, respectively. To determine the effect of thiols on the production of IFN-gamma and IL-4 by splenocytes, cells were incubated in the presence and the absence of N-acetylcysteine (NAC) and stimulated with alphaCD3 or alphaCD3 and IL-12. Augmenting intracellular soluble thiol pools (approximately 2-fold) with 15 mM NAC blocked induction of IFN-gamma and increased production of IL-4 without causing significant changes in intracellular glutathione levels. The effect of NAC on IL-4 production was not linked to an increase in STAT6 phosphorylation, as STAT6 levels were decreased, nor did the increase in IL-4 occur with purified CD4 cells. We found that NAC increased splenocyte IL-4 production via an effect on APCs. We also found that NAC increased two IL-4 relevant transcription factors (AP-1) and NFATc. These studies suggest that increasing intracellular reduced thiol pools decreases IL-12 signaling and IFN-gamma production, while increasing IL-4 production. The sum of these effects may contribute to alterations in the balance between Th1 and Th2 responses in lung diseases associated alterations in intracellular thiol pools.

MeSH: Animals, Trans-Activators, Down-Regulation, Mice, Drug Combinations, Up-Regulation, Mice, Transgenic, Interferon Type II, Interleukin-4, interphase, Interphase, Antigen-Presenting Cells, Cells, Cultured, Cell Nucleus, lymphocyte activation, Lymphocyte Activation, DNA-Binding Proteins, NFATC Transcription Factors, Nuclear Proteins, Adjuvants, Immunologic, Th1 Cells, Mice, Inbred BALB C, STAT6 Transcription Factor, Spleen, Intracellular Fluid, Antigens, CD3, Active Transport, Cell Nucleus

Proteins: STAT6, IL-4, Th1, IFN-gamma, NFATc, CD4, AP-1

Wiki: Sulfhydryl_compounds, Glutathione, Solubility, Interleukin-12, Signal_transduction, Lung_diseases, Transcription_factor_AP-1, Incubators, Cytokinesis, Intracellular, Phosphorylation, Lung, HIV, T-lymphocytes, Transcription_factors, Cytokines, Acetylcysteine

Affiliation: Department of Internal Medicine, University of Iowa, Roy J. and Lucille A. Carver College of Medicine, and Veterans' Administration Medical Center, Iowa City, IA 52242, USA. martha-monick@uiowa.edu

Selective regulation of CD40 expression in murine dendritic cells by thiol antioxidants. PMID: 14511233Related Articles
Authors: Iijima N, Yanagawa Y, Iwabuchi K, Onoé K
Journal: Immunology, 110 (2): 197-205, 2003
Iijima N et al., Immunology, 110 (2): 197-205, 2003
In the present study, we examined the effects of the reducing agents, N-acetyl-l-cysteine (NAC) and reduced glutathione (GSH), on tumour necrosis factor-alpha (TNF-alpha)-induced phenotypic changes in murine DC.
Interaction of CD40 on dendritic cells (DC) with CD40 ligand induces interleukin-12 (IL-12) production by these DC during the antigen presentation. Thus, the level of CD40 expression appears to influence the capability of DC to induce a T helper 1 (Th1) response. However, it is not fully understood how CD40 expression on DC is regulated. In the present study, we examined the effects of the reducing agents, N-acetyl-l-cysteine (NAC) and reduced glutathione (GSH), on tumour necrosis factor-alpha (TNF-alpha)-induced phenotypic changes in murine DC. TNF-alpha markedly increased the expression on DC of major histocompatibility complex (MHC) and the costimulatory molecules, CD40, CD80 and CD86. Both NAC and GSH completely abolished the TNF-alpha-induced enhancement of CD40 expression, but had no considerable effect on the expression of CD80, CD86 and MHC. The marked decrease of CD40 protein with NAC was also detected by Western blotting, but was not associated with the expression level of CD40 mRNA in DC. Thus, NAC appears to reduce CD40 expression on DC by regulating a post-transcriptional pathway. The inhibitory effect of NAC or GSH on TNF-alpha-induced CD40 expression was released by simply removing these agents from the culture. In contrast, culture of TNF-alpha-treated DC with NAC or GSH markedly decreased the expression of CD40 within 12 hr. These results demonstrate that reducing agents selectively, rapidly and reversibly regulate CD40 expression on DC, which may eventually affect the capability of DC for Th1/Th2 polarization.

3:Th1/Th2 balance: the hypothesis, its limitations, and implications for health and disease.
Author: Kidd P
Journal: Altern Med Rev, 8 (3): 223-46, 2003
Kidd P, Altern Med Rev, 8 (3): 223-46, 2003
Mercury depletes glutathione and polarizes toward Th2 dominance.
One theory of immune regulation involves homeostasis between T-helper 1 (Th1) and T-helper 2 (Th2) activity. The Th1/Th2 hypothesis arose from 1986 research suggesting mouse T-helper cells expressed differing cytokine patterns.

This hypothesis was adapted to human immunity, with Th1- and Th2-helper cells directing different immune response pathways. Th1 cells drive the type-1 pathway ("cellular immunity") to fight viruses and other intracellular pathogens, eliminate cancerous cells, and stimulate delayed-type hypersensitivity (DTH) skin reactions. Th2 cells drive the type-2 pathway ("humoral immunity") and up-regulate antibody production to fight extracellular organisms; type 2 dominance is credited with tolerance of xenografts and of the fetus during pregnancy. Overactivation of either pattern can cause disease, and either pathway can down-regulate the other. But the hypothesis has major inconsistencies; human cytokine activities rarely fall into exclusive pro-Th1 or -Th2 patterns. The non-helper regulatory T cells, or the antigen-presenting cells (APC), likely influence immunity in a manner comparable to Th1 and Th2 cells. Many diseases previously classified as Th1 or Th2 dominant fail to meet the set criteria. Experimentally, Th1 polarization is readily transformed to Th2 dominance through depletion of intracellular glutathione, and vice versa. Mercury depletes glutathione and polarizes toward Th2 dominance. Several nutrients and hormones measurably influence Th1/Th2 balance, including plant sterols/sterolins, melatonin, probiotics, progesterone, and the minerals selenium and zinc. The long-chain omega-3 fatty acids EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid) significantly benefit diverse inflammatory and autoimmune conditions without any specific Th1/Th2 effect. Th1/Th2-based immunotherapies, e.g., T-cell receptor (TCR) peptides and interleukin-4 (IL-4) injections, have produced mixed results to date.
MeSH: Animals, Neoplasms, Arthritis, Rheumatoid, Oxidative Stress, HIV Infections, Humans, Multiple Sclerosis, Dendritic Cells, Mycobacterium tuberculosis, Cell Differentiation, cell differentiation, Glucans, Lymphocyte Cooperation
Proteins: APC, interleukin-4, IL-4, EPA, TCR

4:Intracellular thiol redox status of macrophages directs the Th1 skewing in thioredoxin transgenic mice during aging.
Authors: Murata Y, Amao M, Yoneda J, Hamuro J
Journal: Mol Immunol, 38 (10): 747-57, 2002
Murata Y et al., Mol Immunol, 38 (10): 747-57, 2002
We have been proposing the functional distinction of two classes of macrophages (Mp), namely the reductive macrophages (RMp) with high intracellular content of glutathione (GSH) and the oxidative macrophages (OMp) with reduced content.
We have been proposing the functional distinction of two classes of macrophages (Mp), namely the reductive macrophages (RMp) with high intracellular content of glutathione (GSH) and the oxidative macrophages (OMp) with reduced content. At the same time we have been investigating the variation of RMp/OMp balance during aging of mice, especially in relation to the age related onset of autoimmune diseases. In this paper we have investigated

the Th1/Th2 balance of thioredoxin (TRX) transgenic (Tg) mice, with prolonged life longevity, during aging in the context of the intracellular redox status of Mp, which has been hypothesized to be crucial in regulating the Th1/Th2 balance. It was confirmed that peritoneal resident Mp of Tg mice showed the higher GSH/GSSG ratios compared with that of age matched wild type (WT) mice. The predominance of RMp was associated with the sustained maintenance of Th1 prevalence during aging until 2 years in Tg mice, whereas WT littermates showed rapid polarization to Th2 around the age of 8 months. The Tg mice showed elevation of IFN-gamma and reduction of IL-10 with moderate change of IL-4 produced by CD4+ T cells. The WT mice showed inverse changes of IFN-gamma/IL-4 and IFN-gamma/IL-10 ratios during aging. In addition, IL-10 production by Mp was dramatically reduced in aged Tg mice. Thus, TRX Tg mice may be useful to investigate the contribution of the anti-oxidant defense mechanism during aging accompanied with increasing oxidative stress.

MeSH: Animals, Interleukin-10, Interferon Type II, Mice, Inbred C57BL, Gene Expression Regulation, aging, Aging, Macrophages, Peritoneal, Th1 Cells, Th2 Cells, Mice, Inbred BALB C
Proteins: IL-4, IL-10, CD4, IFN-gamma, TRX, thioredoxin, Th1
Wiki: Peritonitis, Transgenes, Sulfhydryl_compounds, Glutathione, Antioxidants, Macrophages, Thioredoxin, Life_support_care, Longevity, Maintenance, Defense_mechanisms, Age_of_onset, Mice, Autoimmunity, Intracellular, Interleukin-4, Oxidation-reduction, Oxidative_stress, Oxides, Prevalence, Autoimmune_Diseases, T-lymphocytes

Affiliation: Basic Research Institute, Ajinomoto Central Research Laboratories, Ajinomoto Co. Inc., 1-1 Suzuki-cho, Kawasaki-ku, 210-0861, Kawasaki, Japan.