understood. TNF-α, a pleiotropic and multifunctional cytokine, transduces regulatory abilities by two distinct cell surface receptors of 55 kd (TNFRp55) and 75 kd (TNFRp75) with most of the known cellular TNF responses attributed to TNFRp55 activation. We used TNFR—deficient mice to characterized the contributions of these receptors in chemical-induced liver toxicity. Single injections of CCl_4 in double knockout mice dose dependently induced larger centrilobular necrosis, prominent destruction of the surrounding hepatocytes and minimal inflammatory response comparing to the same exposure in the background control mice. Liver regeneration, measured as PCNA staining, was impaired in TNFR deficient mice particularly at exposures to high doses of CCl_4. TNFRp55 is sufficient for mediating TNF effects in this model since mice deficient for this receptor demonstrated liver toxicity with similar characteristics as the double TNFR deficient mice. The protective role of TNF-a in CCl_4 -induced liver toxicity may be associated with activation of several transcription factors including NF-kB and AP-1 and generation of secondary inflammatory mediators such as C-C chemokines.

1335 TUMOR NECROSIS FACTOR α MODULATES TRANSFORMING GROWTH FACTOR α EXPRESSION FOLLOWING CHEMICALLY-INDUCED HEPATOTOXICITY.

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Previous studies have shown that Tumor Necrosis Factor-α (TNF-α) expression is increased in the livers of experimental animals following exposure to the hepatotoxin carbon tetrachloride (CCl_4). In addition, administering neutralizing antibodies to TNF-α (anti-TNF-α) prior to exposure to CCl_4 delays the regenerative process of the liver.

We hypothesized that TNF-α may influence liver regenerative processes through modulation of liver derived growth factors. Mice were administered anti-TNF-α prior to CCl_4 treatment. Antibody treatment did not affect the mRNA expression, as assessed by RT-PCR, of hepatocyte growth factor, its receptor c-*met*, epidermal growth factor, epidermal growth factor receptor (EGFR), or acidic fibroblast growth factor. Anti-TNF-α also did not affect liver EGFR number or binding. However, anti-TNF-α decreased the expression of transforming growth factor alpha (TGF-α) approximately 2.5 fold 12 and 24 hours post CCl_4 administration. To confirm this finding ribonuclease protection assays were performed and similar results to that shown with RT-PCR were found. Interleukin-6 (IL6) has been shown to be necessary for liver regeneration following partial hepatectomy, and TNF-α can induce the expression of IL6 in liver. To assess whether TNF-α directly modulates TGF-α expression in the murine liver, recombinant murine TNF-α or recombinant murine IL6 was administered. TNF-α upregulated TGF-α expression approximately four fold above control levels, whereas IL6 did not affect TGF-α mRNA expression 90 minutes post injection. Taken together, these data indicate that TNF-α modulates the expression of TGF-α in the liver following hepatotoxic injury with CCl_4, and that this modulation is independent of IL6 induction.

1336 ENDOGENOUS METALLOTHIONEIN CAN ALTER AN ANTIGEN SPECIFIC HUMORAL RESPONSE.

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Metallothionein (MT) acts as a reservoir of essential heavy metals, it can regulate Zn-dependent transcription factor activity, scavenge free radicals, and participate in the cellular defense against toxic heavy metals. These various roles are clearly essential to cell homeostasis, thus it is somewhat unexpected that mice deficient in MT-1 and MT-2 synthesis are without a profound effect on phenotype. This may be due to the fact that MT's role in biological systems is most important during periods of cellular stress, and that other mechanisms substitute during periods of normal cellular activity. In previous work, we have shown that exogenous MT can reduce a specific immune response to a T-dependent antigen when simultaneously presented with antigen to an animal. We extend our findings here to address the effect of the pool of MT that is synthesized as a consequence of immune cell responses to antigen. The absence of MT-1 and MT-2 in MT-null animals correlates with a twofold increase in antibody titer to the T-dependent antigen (ovalbumin, OVA). The onset of this response remains unaltered. Moreover, this effect appears to depend, at least partially, on endogenous extracellular MT, since injection of a monoclonal anti-MT antibody (clone UC1MT) enhances the humoral response to OVA in animals with a normal complement of MT genes when compared to syngeneic animals immunized in the presence of an isotype-matched antibody control. Our experiments suggest that MT can be a potent modifier of humoral responses, and that manipulation of MT levels during autoimmune or inflammatory disease may have beneficial consequences.

1337 ROLE OF GLUTATHIONE IN LYMPHOCYTE REDOX BALANCE AND FUNCTIONAL DEVELOPMENT.

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Lymphocytes encounter oxidative stress at sites of inflammation, in association with HIV infection, and with exposure to certain immunotoxicants. We investigated the role of the cellular antioxidant glutathione (GSH) in the maintenance of redox homeostasis and cellular function of T lymphocytes. Human peripheral T cells treated with a short pulse of H_2O_2 prior to stimulation by cell surface receptor engagement demonstrated a greatly reduced proliferative response, dose-dependent decrease in cell activation markers, and impaired cytokine production. H_2O_2 treatment rapidly activated GSH biosynthesis by glutamate cysteine ligase (GLCL), which led to rapid replenishment of intracellular GSH. We found that normal resting T cells were much more sensitive to H_2O_2 treatment than T cells which had been previously activated with phytohemaglutinin and undergone a round of proliferation (PHA blasts). The PHA blasts were capable of proliferation upon restimulation following pulses of H_2O_2 at concentrations 10 to 20-fold greater than those which completely inhibited proliferation of normal T cells. GLCL was induced by T cell activation, and expression of both the catalytic and regulatory subunits was increased by day 1 following stimulation. However by day 5, expression of both GLCL subunits had returned to levels similar to those found in unstimulated T cells. The GLCL enzyme activation following H_2O_2 treatment was also the same for T cells and day 5 PHA blasts. Therefore while GLCL is induced by lymphocyte activation, this induction is transient and does not account for the increased resistance to oxidative stress seen in PHA blasts. Increased GLCL activity may protect lymphocytes early after activation, whereas other inducible enzymes may be involved in the sustained protection seen in previously activated T cells. This work was supported by Bristol-Myers Squibb and National Institutes of Health grants ES04696 and ES07032.

1338 IMMUNODEFICIENCY INDUCED BY METHYLMERCURY IN C57BL/6 MICE IS RELATED TO INCREASE OF FAS-MEDIATED APOPTOSIS IN SPLENIC AND THYMIC CD4+ T CELLS.

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Methylmercury chloride (MeHgCl) is known to reduce both humoral and cell-mediated immune responses, rendering animals more sensitive to infectious diseases. The mechanism(s) by which mercury elicits immunodeficiency remains unclear. We have postulated that MeHgCl increase, at subtoxic doses, the apoptosis process in T cells from sensitive C57BL/6 mice. We have studied, *in vitro*, the number of apoptotic cells in splenic and thymic T subpopulations exposed to MeHgCl by double immunostaining with anti-CD4, anti-CD8, anti-Thy1 or propidium iodide (IP). Cytofluorometric analysis revealed that low doses (0.001 to 0.01 mM) of MeHgCl increased apoptosis, as defined by FSC/SCC, IP staining and the TUNEL method, in total and in T splenic cells while toxic effects occurred with higher doses (0.1 to 1 mM). ConA-activated splenic cells were more sensitive to MeHgCl-induced apoptosis, particularly the CD4+ subpopulation. Apoptosis was also increased in thymic mature CD4+ cells treated with lower concentrations of MeHgCl. Cell cytotoxicity analysis showed that MeHgCl acts by increasing the apoptosis induced by anti-Fas antibodies. In addition, the splenic CD4+ Vb8 subset was preferentially depleted whereas CD4+ Vβ6 cells increased. These results suggest that immunodeficiency induced by MeHgCl may be caused by induction of an apoptotic process in thymic and splenic T cells via the Fas antigen.

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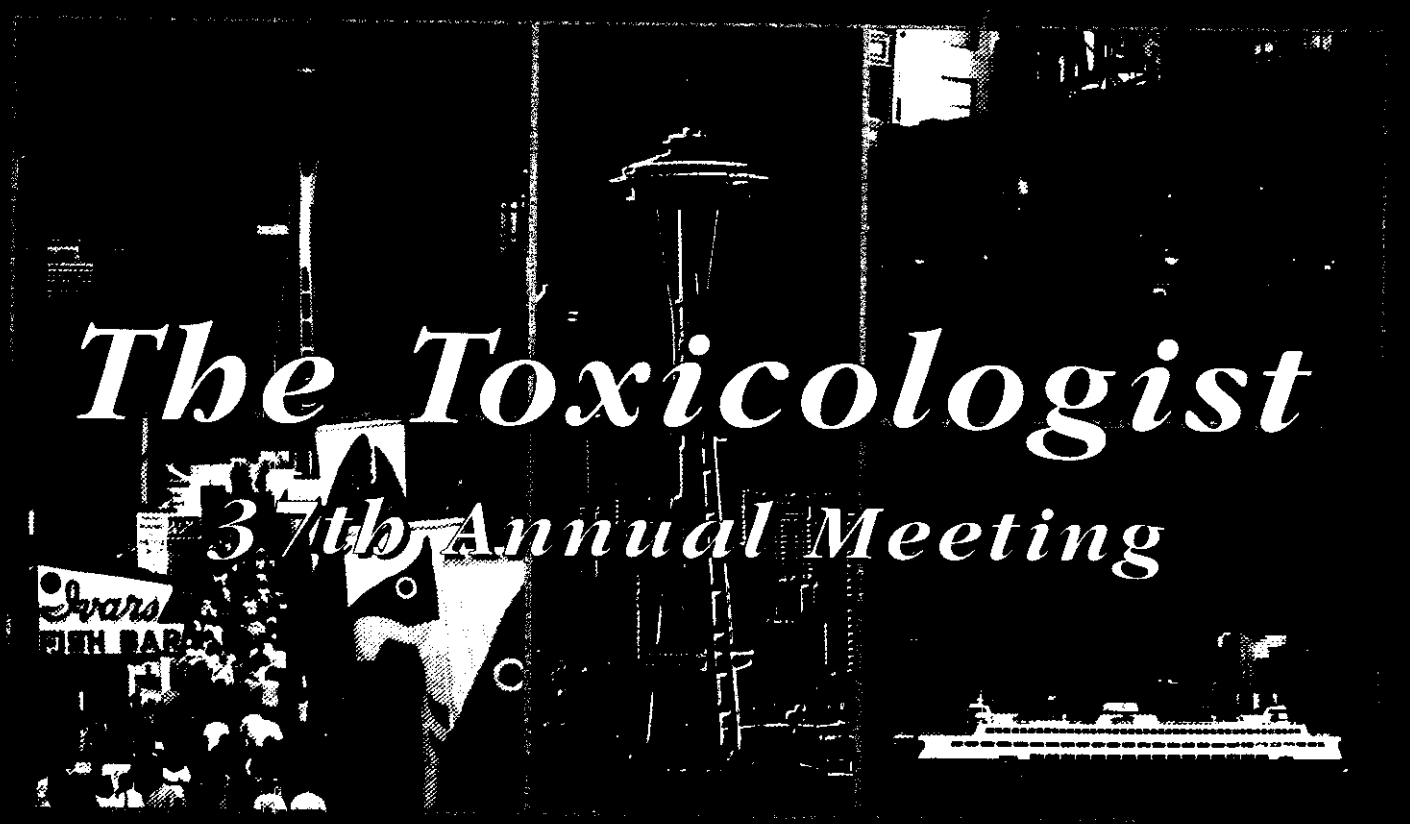

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Preface

This issue of *The Toxicologist* is devoted to the abstracts of the presentations for the symposium, platform, poster / discussion, workshop, roundtable, and poster sessions of the 37th Annual Meeting of the Society of Toxicology, held at the Washington State Convention Center, Seattle, Washington, March 1-5, 1998.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 407.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 433.

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