Role of Interleukin 6 (IL-6) in Protection from Lethal Irradiation and in Endocrine Responses to IL-1 and Tumor Necrosis Factor

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Summary

Primary responsibility for the induction of various acute phase reactions has been ascribed to interleukin 1 (IL-1), tumor necrosis factor (TNF), or IL-6, suggesting that these cytokines may have many overlapping activities. Thus, it is difficult to identify the cytokine primarily responsible for a particular biologic effect, since IL-1 and TNF stimulate one another, and both IL-1 and TNF stimulate IL-6. In this work, the contribution of IL-6 in radioprotection, induction of adrenocorticotropic hormone (ACTH), and induction of hypoglycemia was assessed by blocking IL-6 activity. Administration of anti-IL-6 antibody to otherwise untreated mice greatly enhanced the incidence of radiation-induced mortality, indicating that like IL-1 and TNF, IL-6 also contributes to innate resistance to radiation. Anti-IL-6 antibody given to IL-1-treated or TNF-treated mice reduced survival from lethal irradiation, demonstrating that IL-6 is also an important mediator of both IL-1- and TNF-induced hemopoietic recovery. A similar IL-1/IL-6 interaction was observed in the case of ACTH induction. Anti-IL-6 antibody blocked the IL-1-induced increase in plasma ACTH, whereas recombinant IL-6 by itself did not induce such an increase. Anti-IL-6 antibody also mitigated TNF-induced hypoglycemia, but did not reverse IL-1-induced hypoglycemia. It is, therefore, likely that TNF and IL-1 differ in their mode of induction of hypoglycemia. Our results suggest that an interaction of IL-6 with IL-1 and TNF is a prerequisite for protection from radiation lethality, and its interaction with IL-1 for induction of ACTH.

The ability to utilize cytokines clinically relies on identifying the specific pathophysiologic functions of individual cytokines in the host's defenses. With the availability of pharmacological quantities of recombinant cytokines, sufficient to be evaluated in animal models, it was originally anticipated that individual cytokines could be ascribed specific biologic activities. Indeed, initial studies documented that many inflammatory processes could be reproduced by systemic administration of rIL-1 or of rTNF-α, establishing these two cytokines as major inflammatory mediators (1, 2). Subsequent studies, however, suggested that many of the actions of IL-1 or TNF, including stimulation of production of acute phase proteins by hepatocytes (3, 4), stimulation of the hypothalamic-pituitary-adrenal axis (5–7), or hematopoietin 1 effects (8, 9), can be mimicked by IL-6 (10–14).

Because IL-1 and TNF induce IL-6 (15, 16), the possibility that these relatively toxic cytokines can be replaced by the much less toxic IL-6 presents an obvious clinical advantage. To examine this possibility, we evaluated the contribution of IL-6 in several IL-1- and TNF-mediated activities, by testing

the effect of anti-IL-6 antibody (20F3) in vivo. Our results show that IL-6 is an essential contributor to natural resistance to lethal irradiation, to IL-1- and TNF-induced recovery from lethal irradiation, to induction of ACTH[1] by IL-1, and to TNF-induced hypoglycemia. However, IL-6 did not induce any of the aforementioned effects when administered by itself to mice (15, 17, and R. Neta, unpublished results). Therefore, we propose that obligatory interaction of IL-1 or TNF with IL-6 may be a prerequisite for some of the biological effects of these inflammatory cytokines.

Materials and Methods

Mice. CD2F₁ male and C3H/HeN female mice were purchased from the Animal Genetics and Production Branch, National Cancer Institute, National Institutes of Health (Frederick, MD). Mice were handled as previously described (15).

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[1] *Abbreviation used in this paper:* ACTH, adrenocorticotropic hormone.

Cytokines. Recombinant human IL-1 (rHuIL-1α; 117–271 Ro 24-5008; lot IL-1 2/88; sp act 3 × 10⁸ U/mg) was kindly provided by Dr. Peter Lomedico, Hoffmann-La Roche, Inc. (Nutley, NJ). Recombinant murine TNF (rmTNF-α; lot 4296-17; sp act 2 × 10⁸ U/mg, as assayed on L929 cells in our laboratory) was kindly provided by Dr. Grace Wong, Genentech Inc. (So. San Francisco, CA).

Antibodies. Rat mAb to mouse rIL-6 (MP5 20F3) was prepared using semi-purified Cos-7 mouse IL-6 as an immunogen, as previously described (18). The isotype control, rat mAb to β-galactosidase (GL113) was used. A rat monoclonal IgG1, anti-IL-1 receptor antibody (35F5) was previously described (19). Chromatographically purified rat IgG (Sigma Chemical Co., St. Louis, MO) was used as an additional control. The antibodies and recombinant cytokines were diluted in pyrogen-free saline on the day of injection. Antibodies were given intraperitoneally 6–20 h before intraperitoneal injection of the cytokines.

Irradiation. Mice were randomized, placed in plexiglass containers, and were given whole-body irradiation at 40 cGy/min midline tissue dose, by bilaterally positioned ⁶⁰Co elements. The radiation field was uniform within ±2%. The number of surviving mice was recorded daily for 30 d.

Immunoenzymetric Assay for IL-6 Determinations in the Serum. Serum samples obtained at 2–4 h after cytokine injections were assayed for IL-6 using a two-site sandwich immunoassay as described (18). The threshold sensitivity of this assay was 50 pg/ml.

Measurements of ACTH in Plasma. ACTH was assayed in plasma from decapitated mice using an ¹²⁵I RIA kit (INCSTAR Corp., Stillwater, MN) as previously described (17). The ACTH antibody used in this assay is derived from rabbits immunized against human ACTH1-24, a region identical in human and murine ACTH. The threshold sensitivity of this assay was 8 pg/ml.

Glucose Determination. Levels of glucose in serum samples were measured using glucose oxidase reagent kit (KODAK Ektachem Clinical Chemistry Slide) as described elsewhere (20). In this assay, hydrogen peroxide is detected based on its oxidant activity in a peroxidase-catalyzed oxidative-coupling reaction in the presence of chromogen to form a dye. The intensity of the dye is measured at 540 nm. The Kodak Ektachem-700 Analyzer was calibrated before each assay.

Statistical Analysis. Statistical evaluation of the results was carried out using χ^2 analysis and analysis of variance followed by Fisher protected least significant difference test.

Results

The Role of IL-6 in Innate Radioresistance. Previous work has indicated that administration of anti-IL-1R or anti-TNF antibody results in increased mortality of irradiated mice (21). To examine whether endogenously produced IL-6 contributes to innate radioresistance, anti-IL-6 antibody was given to normal, untreated mice before irradiation. Such treatment greatly enhanced the incidence of mortality, from 35 to 80% (Fig. 1). Thus, endogenously produced IL-6 clearly contributes to the survival of mice recovering from radiation injury.

Comparison of IL-1 and TNF for Induction of IL-6. We have previously shown that pretreatment with IL-1 or TNF results in enhanced survival of lethally irradiated mice. Since IL-1 and TNF are known to induce IL-6, we next sought to determine the relative contribution of IL-6 in TNF- and in IL-1-treated mice. We first determined the levels of IL-6 in cir-
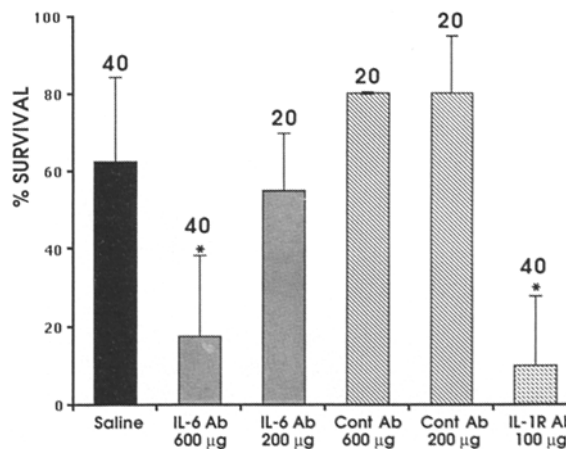

Figure 1. CD2F₁ mice received 0.5 ml/mouse i.p. of saline, anti-IL-6 Ab, control GL113 Ab, or anti-IL-1R Ab 16 h before exposure to 825 cGy of radiation. The number at the top of the bars indicates the total number of animals in four independent experiments. *Significantly different ($p < 0.001$) from saline control.

culation of IL-1- or TNF-treated mice (Table 1). Consistent with previous findings (15), detectable serum IL-6 levels appeared even after doses as low as 10 ng of IL-1, but microgram doses of TNF were required to induce measurable circulating IL-6. Consequently, a dose of 600 µg/mouse of anti-IL-6 antibody neutralized serum IL-6 in mice given 5 µg/mouse of TNF, but this dose was insufficient to completely block serum IL-6 in mice given 300 ng of IL-1 (Table 1). Therefore, in subsequent studies of the contribution of

Table 1. *Effect of Anti-IL-6 Antibody on Serum Titers of IL-1- or TNF-induced IL 6*

Cytokine treatment	Saline	Anti-IL-6 antibody	Control antibody
		pg/ml	
Saline	<50	<50	<50
IL-1 (20 ng)	745	–	532
IL-1 (50 ng)	1,198	<50	–
IL-1 (100 ng)	1,383	<50	–
IL-1 (300 ng)	3,623	82	–
TNF (5 µg)	121	<50	209

CD2F₁ mice were given saline injections, anti-IL-6 Ab (600 µg/mouse), or control Ab (GL113, 600 µg/mouse), followed by cytokine treatment 16 h later, and were bled at 2 and 4 h after cytokine administration. Sera from pools of three mice/group were assessed for IL-6. The levels of IL-6 are shown for 2 h after IL-1 injections and 4 h after TNF injections (since these were the optimal levels, with the exception, however, for anti-IL-6 and 300 ng of IL-1 where the results of two experiments of 4 h of bleeding and one experiment of 2 h of bleeding were combined). The results are means of two to four experiments (individuals values varied within ±20%).
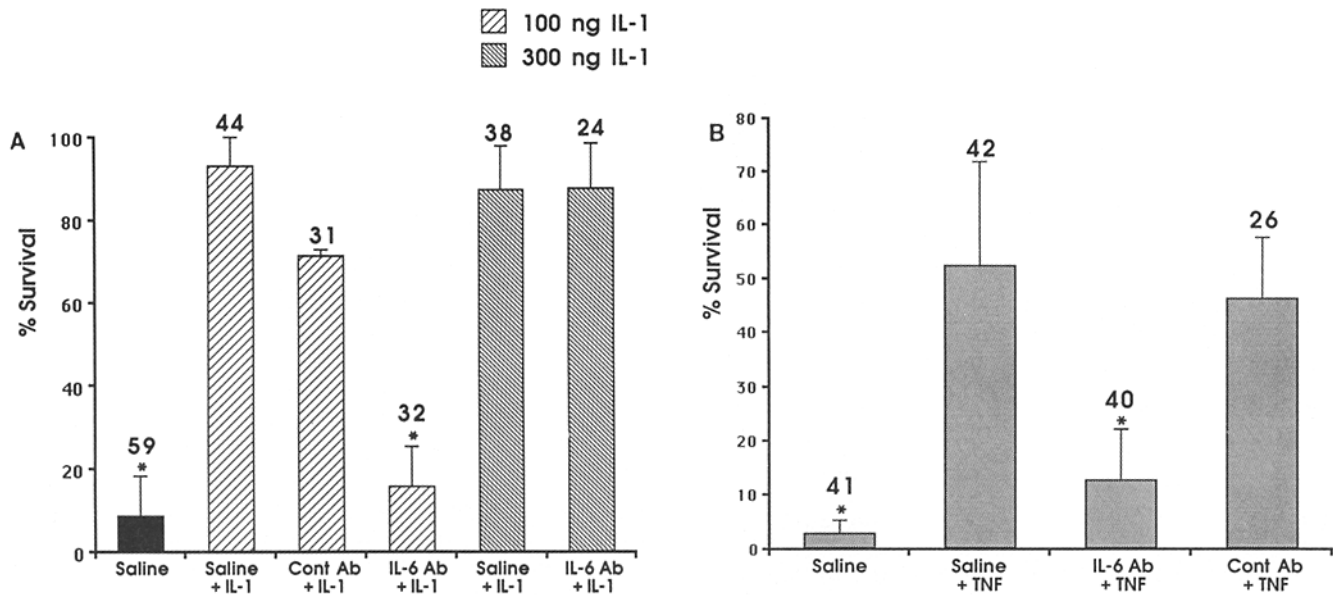
Figure 2. CD2F₁ mice received 600 µg anti-IL-6 or control Ab (GL113 or rat Ig) injections 16 h before treatment with IL-1 (*A*) or 5 µg TNF (*B*), and 20 h later were exposed to 950 cGy of radiation. *Significantly different (*p* < 0.01) from saline + IL-1 group, and saline + TNF group, respectively.

IL-6 in induction of protection from radiation lethality, hypoglycemia, and ACTH release, doses of IL-1 and TNF were used that could be neutralized by the anti-IL-6 antibody.

The Role of IL-6 in IL-1- and TNF-enhanced Survival from Lethal Irradiation. Both IL-1 and TNF promote survival from radiation lethality (22, 23). To assess the role of IL-6 in mediating the recuperative effects of these two cytokines, mice were given anti-IL-6 antibody 6–20 h before administration of IL-1 (100 ng) or TNF (5 µg). The results (Fig. 2, *A* and *B*) indicate that anti-IL-6 antibody can completely block both IL-1- and TNF-enhanced survival from lethal irradiation.

The Role of IL-6 in IL-1- and TNF-induced Hypoglycemia. As previously demonstrated, both IL-1 and TNF induce, within 2–4 h, hypoglycemia in mice (24). IL-1, however, is much more potent than TNF in inducing hypoglycemia, since as little as 20 ng of IL-1 induced hypoglycemia, whereas >5 µg of TNF was required to induce a similar decrease in blood glucose levels. Anti-IL-6 antibody did not change the magnitude of IL-1-induced hypoglycemia (Fig. 3 *A*). In contrast, the same dose of anti-IL-6 resulted in a significant reversal of TNF-induced hypoglycemia (Fig. 3 *B*).

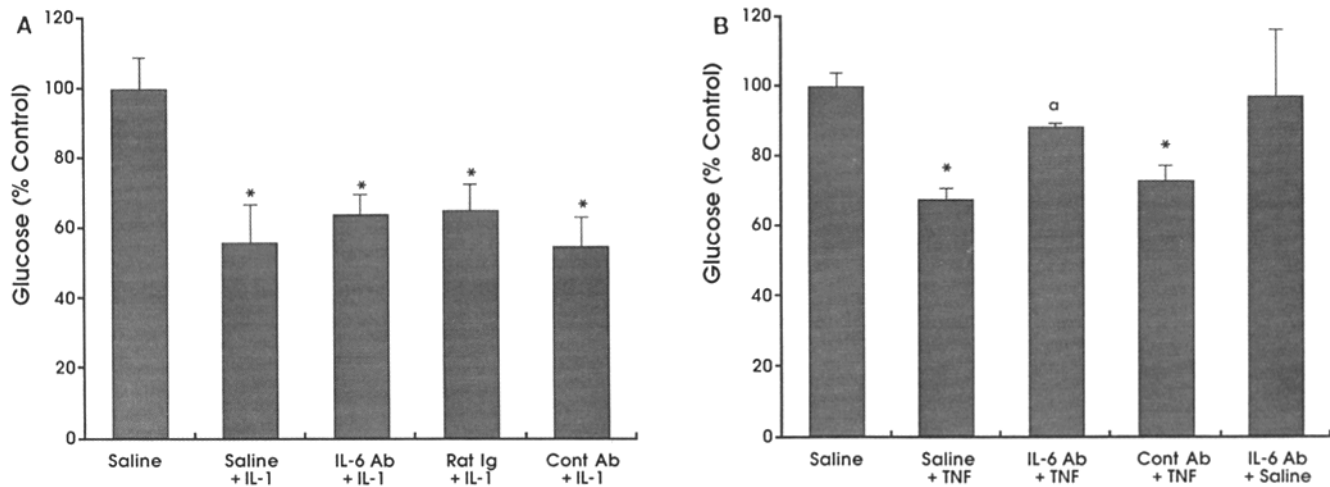*IL-1/IL-6 Interaction in ACTH Induction.* Our previous work

Figure 3. CD2F₁ mice received Ab (600 µg/mouse) 16 h before 20 ng IL-1 (*A*) or 5 µg TNF injection (*B*). The results are means ± SEM of three independent experiments, each one with a pool of three to five mice, for TNF and individual bleedings of seven mice from two independent experiments for IL-1. *Significantly different (*p* < 0.05) from saline control group. ªSignificantly different (*p* < 0.05) from saline + TNF.
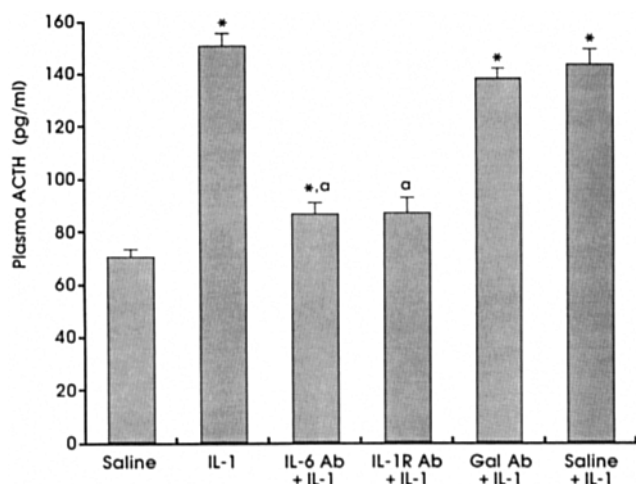
Figure 4. C3H/HeN mice were given Ab (600 μg/mouse) 16 h before 100 ng IL-1 injection. The results are means ± SEM of three independent experiments, each with five mice/group assayed individually. *Significantly different (p < 0.01) from saline control. ªSignificantly different (p < 0.01) from IL-1 treatment.

determined that IL-1 and IL-6 interact synergistically to induce circulating ACTH (17). To assess the contribution of IL-6 in IL-1-induced ACTH release, mice were given anti-IL-6 antibody before receiving IL-1. As shown in Fig. 4, anti-IL-6 antibody blocked the ACTH response to IL-1. Since no consistent elevation of plasma ACTH was detected in TNF-treated mice, similar experiments using anti-IL-6 antibody were not conducted in TNF-treated mice.

Discussion

The availability of neutralizing antibody to cytokines allows the assessment of the contribution of individual cytokines and their interaction in host defenses in vivo. For example, our previous studies demonstrated that administration of anti-IL-1R and anti-TNF antibody to normal mice caused greater mortality upon exposure of these mice to lethal radiation (21). Moreover, anti-IL-1R antibody not only blocked IL-1-induced, but also TNF-induced protection from lethal irradiation. Conversely, anti-TNF antibody also reduced IL-1-induced protection from radiation death, suggesting that these two cytokines induce one another in vitro and in vivo (25–28), and that their interaction is necessary for enhanced survival from lethal irradiation.

IL-6 not only fails to induce IL-1 or TNF, but actually has been reported to suppress their production (29, 30). Thus, as we have previously observed, administration of IL-6 alone before irradiation would not be expected to lead to enhanced survival and would actually reduce survival from lethal irradiation (15). Despite this, injection of anti-IL-6 antibody in this study results in increased mortality of irradiated, normal mice as well as irradiated TNF- or IL-1-treated mice. These observations suggest that IL-6 participates in both innate as well as IL-1- and TNF-induced resistance to radiation lethality.

The failure of IL-6 by itself to improve radiation survival indicates that the activity of IL-6 only becomes manifest in the course of interaction with other cytokines. This hypothesis is supported by our earlier report that IL-6 given together with suboptimal doses of IL-1 resulted in synergistically enhanced survival from lethal irradiation (15). Since radiation itself induces the production of endogenous IL-1 (31–33) and TNF (34, 35), their presence would be expected to result in endogenous production of IL-6. Consequently, the interaction of all three cytokines, i.e., IL-1, TNF, and IL-6, would contribute to innate resistance of normal mice to radiation lethality.

When given individually, IL-1 and TNF induce significant protection from radiation-induced lethality and induce hypoglycemia. One possible explanation for the observed lower potency of TNF in both of these biologic responses may be related to its much lower capacity to induce IL-6 (Table 1). Even 20 ng dose of IL-1 induced higher levels of IL-6 than 5 μg of TNF. Our results indicate that 600 μg of anti-IL-6 antibody blocked radioprotection and ACTH induction with 100 ng IL-1, whereas the hypoglycemia induced with 20 ng IL-1 was not significantly affected by this antibody. In contrast, TNF-induced hypoglycemia can be reduced by anti-IL-6 antibody. This suggests that the mechanisms of induction of hypoglycemia by these two cytokines differ. Alternatively, induction of IL-6 or distribution of antibody may vary in different tissues. Our previous work, showing a synergistic interaction of IL-1 and TNF in induction of hypoglycemia (24), supports the first of these two hypotheses.

The ability to block IL-1-induced release of ACTH with anti-IL-6 antibody further extends our previous findings, which showed that IL-1 and IL-6 synergize to induce ACTH (17). In that study, doses of 10 μg of IL-6 induced only minimal changes in plasma ACTH, whereas IL-1 alone induced ACTH within 2 h (a time interval also necessary for IL-1 induction of IL-6) (15). The combination of IL-1 and IL-6 induced optimal levels of ACTH within 30 min. Thus, together with our present results, these observations strongly support the hypothesis that the simultaneous presence of both IL-1 and IL-6 is necessary for release of ACTH in vivo. Our attempts to observe similar elevation of plasma ACTH after administration of 5 μg TNF to C3H/HeN mice were unsuccessful (Perlstein and Neta, unpublished results). Thus, TNF may not induce levels of IL-6 sufficient to induce ACTH. A previous report, which showed that rats given IL-6 alone have elevated plasma ACTH (13), may be explained either by a lower requirement for this interaction in rats or, alternatively, by the possible presence of sufficient endogenous levels of IL-1 in this species.

In conclusion, these results serve to reconcile the apparently conflicting observations by many laboratories concerning the relative importance of the contributions of IL-1, TNF, and IL-6 to a variety of pathophysiological reactions. The interdependence and synergistic interactions of these three cytokines are apparently mandatory for many of their biological effects.

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