INTRODUCTION

Natural Killer (NK) cells constitute a class of unprimed lymphocytes, cytotoxic to certain types of tumor cells, virus infected cells and some rapidly proliferating populations of cells of hemopoietic origin. It is believed that NK cells may play an important role in (a) immune surveillance against spontaneously arising tumor cells in vivo, (b) immunity to certain viruses and parasites and (c) control of hemopoiesis.

The cytotoxic activity of NK cells can be regulated by a number of biological response modifiers like the interleukins and interferons etc. Interleukin-2 (IL-2) is a T cell derived lymphokine which is produced primarily by activated T-helper cells in response to antigens or mitogens. IL-2 is known to augment the cytotoxic activity of T lymphocytes, macrophages and NK cells etc. by acting through the IL-2 receptor present on these cells. The effect of IL-2 on the NK activity oh human and murine systems has been widely reported in literature. Prolonged culture of human peripheral blood mononuclear cells and murine spleen cells with high doses of IL-2, induces very high levels of lytic activity against NK susceptible and resistant target cells
but not against normal non cancerous cells. This effect of IL-2 has been exploited to generate populations of lymphokine Activated Killer (LAK) cells, with a wider target specificity than that of NK cells and very high levels of cytotoxic activity, to be used for immunotherapy of cancers.

While the cells mediating NK activity have also been described in the rat system, the effect of IL-2 on the levels of NK activity in cultured rat spleen cells has not been described in literature. For the present thesis a detailed study of the effect of IL-2 on rat NK activity has been made. Our initial results show that NK levels in cell preparations derived from various lymphoid organs of rat failed to be boosted by IL-2 whereas in parallel experiments, IL-2 could induce marked augmentation of NK activity in human and murine lymphocyte preparations. Several rat strains were examined for the effect of IL-2 and the results indicated that despite the strain dependant variations, in general, IL-2 induced NK activation in the rat system remained poor at best. Interestingly rat spleen cells utilized IL-2 and proliferated in response to this lymphokine but did not generate high lytic activity. Attempts were made to elucidate the mechanism of lack of optimal IL-2 induced NK activation in rat spleen cells. We have found that rat spleen cells in culture constitutively secrete a suppressor factor(s). The suppressor factor could prevent the activation of IL-2 NK activation in mouse spleen cells. High doses of L-2 were
unable to overcome the effect of the suppressor factor. We have attempted to characterize and purify the suppressor factor. This data points to the suppressor factor being a small molecular weight entity which can bind to a large molecular weight factor. Release of the factor could be blocked by Indomethacin, an inhibitor of the cyclooxygenase pathway of prostaglandin biosynthesis. Moreover in the presence of indomethacin, IL-2 could induce high levels of cytotoxic activity in cultured rat spleen cells. Indomethacin mediated reversal of suppressor activity suggests that prostaglandins could be the suppressor factor released by rat spleen cells and could be responsible for the observed lack of optimal IL-2 induced NK activation of rat spleen cells.

Interestingly we have also found that the rat bone marrow cells do not have significant basal NK activity and cannot be induced to become cytotoxic by IL-2. In contrast high cytolytic activity could be induced in mouse bone marrow cells by IL-2. Unlike rat spleen cells, rat bone marrow cells did not secrete suppressor activity and cytolytic activity could not be induced in these preparations even in the presence of indomethacin. The mechanism of lack of IL-2 induced NK activation therefore appears to be different in rat spleen and bone marrow cells.