Recombinant Interleukin-1α, Interleukin-2 and M-CSF-1 enhance the survival of newborn C57BL/6 mice inoculated intraperitoneally with a lethal dose of herpes simplex virus-1

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Summary. Recombinant Interleukin-1α (IL-1α), Interleukin-2 (IL-2) and recombinant macrophage colony-stimulating factor-1 (M-CSF-1) as well as combinations of IL-2 and M-CSF-1 were studied for their ability to protect seven-day-old C57BL/6 mice against HSV-1 infection. Treatment of the mice with IL-2, M-CSF-1 or combinations of IL-2 and M-CSF-1 significantly increased survival rates. Treatment with IL-1α (10 U and 100 U/mouse) was most effective in protection against HSV-1, resulting in significantly increased survival rates more than four times greater than the survival rate of the infected control group.

Introduction

Disseminated herpes simplex virus-1 (HSV-1) infection of newborns is a severe condition with mortality reaching as high as 15–20% in human neonates [13]. The outcome of HSV-1 infection can be influenced by the immunocompetency of the host. Defects in the immune system of neonates, possibly resulting in increased susceptibility to HSV-1 infection, have been identified both in humans and in the murine model. In the latter, most studies have been conducted with C57BL/6 mice which, at the age of four weeks, are resistant to intraperitoneal infection with HSV-1 as adults, but as newborns are highly susceptible [15, 32, 41]. Human studies suggest a delayed production of anti-HSV-1 antibody in neonates with low antibody-dependent cellular cytotoxicity (ADCC) as compared to adults [18]. The murine model reveals that newborn mice also have poor antibody responses to exogenous antigens [22]. However, administration of large doses of anti-HSV-1 antibodies immediately before or after infection with HSV-1 may alter the result of the infection [1, 3, 8, 26, 34]. Other immunologic defects previously described in newborn mice include defective macrophage function and impaired T-cell function, characterized by altered lym-
phokine production [14, 17]. Clearance of the virus from the peritoneum following intraperitoneal (i.p.) infection is accomplished largely by peritoneal macrophages [34]. The state of activation [2] and differentiation [35] of macrophages affects their ability to restrict HSV-1 replication in vitro [31]. When mature macrophages are absent from the peritoneum, the virus is able to penetrate the central nervous system, resulting in a lethal encephalitis in the mouse model [42]. Macrophages of neonate animals are unable to restrict viral replication [17]. Numerous attempts have been made to overcome these immunological defects. The transfer of peritoneal cells from nonimmune syngeneic adult mice to newborns results in reconstitution of the ability to produce antibodies [19]. This appears to be due to both macrophages and helper T-cell populations although the latter may be replaced with soluble helper T-cell products [19]. Lethal HSV-1 infection may be prevented either by administration of macrophages and T-cells or macrophages and T-cell-lymphokine-containing fraction [14]. T-cells may also be replaced with human recombinant interleukin-2 (IL-2) [14].

IL-1 plays an important role in local and generalized inflammatory and immune responses and has a wide spectrum of biological activities, including the induction of T lymphocyte proliferation and the initiation of the acute phase response [5, 6]. It also stimulates the production of IL-2, IL-3, IL-6 and the interferons [6] and acts in the augmentation of the immune response to antigens. Although originally described as a product of activated phagocytic cells, studies have shown that it is synthesized by numerous cell types. Expression of the IL-1 gene is induced in the course of antigen presentation to T-cells [21]. IL-1 activity is encoded by two different genes, IL-1α and IL-1β. The murine cDNAs were cloned and shown to detect RNA species of 2.1 and 1.4 kb, respectively, by the Northern blot technique [9, 24]. Both species share the same range of biological activities [4, 6, 36] and bind to the same 80 kDa receptor [7].

IL-2 is secreted by T lymphocytes upon stimulation with mitogen or antigen and has effects on several immune functions including enhancement of natural killer (NK) cell activity, the induction of lymphokine-activated killer (LAK) cells and stimulation of interferon-γ production [40]. It also stimulates antiviral cytotoxicity of both adult and neonate human cells [20]. Human recombinant IL-2 (rIL-2) has previously been shown to protect against acute HSV-2 genital infections in guinea pigs [40] and is an effective immune therapy in neonatal mice when administered one day prior to infection [16]. Furthermore, the production of fully differentiated T-cells has an absolute requirement for IL-2. Resting T-cells do not make IL-2 nor do they respond to external sources of the factor. Both stimulation of IL-2 production and display of the IL-2 receptor requires the introduction of antigen.

Macrophage colony-stimulating factor (M-CSF-1) belongs to a group of growth factors that stimulate proliferation and differentiation of bone marrow progenitor cells and may also stimulate mature cells. Its primary role is macrophage activation [39]. Although IL-2 protection of newborn mice from HSV-