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The Potential Role of Serum Ferritin in the Pathogenesis of Acquired Immune Deficiency Syndrome (AIDS)

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Abstract — Elevated serum ferritin levels have been observed in several disease states including various malignancies, inflammatory states, and the acquired immunodeficiency syndrome (AIDS). This discussion will examine the normal sequence of events in T cell activation and proliferation, as well as the various defects in these events, and monocyte/macrophage and NK cell activity seen in AIDS patients. Further, the potential role of a serum suppressor factor as a contributor to the profound immunosuppression seen in AIDS will be discussed, as will evidence suggesting that ferritin may be this factor. A model is presented to explain mechanisms by which ferritin might suppress immune function and further studies to elaborate these mechanisms are proposed.

Introduction

Elevated serum ferritin levels have been noted in patients with various malignancies including Hodgkin's disease (1, 2), breast cancer (3, 4) and neuroblastoma (5), and more recently in patients with AIDS and AIDS-related complex (ARC) (6). This discussion will focus on the graded elevation of ferritin levels seen in patients with ARC and AIDS (6), and propose a model for the role of ferritin in the pathogenesis of AIDS.

The etiologic agent responsible for the acquired immune deficiency syndrome (AIDS) is the human T lymphotropic virus type III (HTLV-III) (7, 8), now known as the human immunodeficiency virus (HIV). HIV binds to cells bearing the CD4 (T4) antigen on the cell surface, and in so doing is able to infect helper T lymphocytes (9, 10), monocyte/macrophages (11, 12), epidermal Langerhans cells (13), and neurons and glial cells in the CNS (9, 14).

T-cell activation

Patients with AIDS have a variety of defects in immune function, which for the most part may be explained by depletion and/or functional disruption of helper/inducer T lymphocytes. Of particular concern here are the defects in T lymphocyte, as well as natural killer (NK) and monocyte/macrophage function. Before considering the various defects, the normal sequence of events in T cell activation will be discussed. Activation of T lymphocytes requires

interaction of ligand with cell surface receptors and generation of intracellular signals, which in turn lead to the expression of activation markers (i.e. receptors for interleukin-2 and transferrin) (15–18), interleukin-2 (IL-2) production (19), and ultimately T cell proliferation Synthesis and expression of the interleukin-2 receptor (IL-2R) is an early event (20), while IL-2 production peaks within 24 hours of antigen stimulation (15) and transferrin receptor (Tf-R) expression peaks after 48 hours post-exposure (20). IL-2 regulates the expression of its own receptors as well as those for transferrin (Tf) (18, 21–23). IL-2 and transferrin receptor expression appears to be required for DNA synthesis and proliferation by activated T cells (18), as is the interaction of IL-2 (19, 24) and transferrin (18, 25) with these receptors. Monoclonal antibodies against the Tf-R inhibit cell growth *in vitro* (26–29), and inhibit the generation of cytotoxic T lymphocytes (30). Cytotoxic T lymphocytes produce interferon-γ (IFN-γ) in response to antigens or mitogens (38, 39), under the positive influence of IL-2 (33, 35). IL-2 is produced by helper T lymphocytes (40, 42).

T cell defects

AIDS patients have several qualitative defects in the activation and proliferation of T lymphocytes, in addition to the well documented lymphopenia and inversion of the helper/suppressor T lymphocyte ratio (36–43). These defects include decreased IL-2 production (36, 39, 44) and IL-2R expression (36, 38, 44), as well as decreased IFN-γ production (37, 45, 46) and cytotoxic T cell activity (47). More general measures of T lymphocyte function show decreased *in vitro* proliferation in response to mitogens (36–39, 41–43, 48), antigens (41, 43, 48), or alloantigens (40, 43), as well as decreased E-rosette formation (42, 43, 48) and skin test reactivity (43, 48). Exogenous IL-2 can partially restore mitogen-induced lymphocyte proliferation (39) and cytotoxic T cell activity (47) *in vitro*. *In vivo*, infusions of IL-2 cause a polyclonal expansion of T cells and IL-2R expression, but apparently have no impact on transferrin receptor expression or subsequent mitogen-induced T cell proliferation *in vitro* (49). IL-2 enhances IFN-γ production by normal lymphocytes, but not those from AIDS patients (46). It appears then, that in addition to being decreased in total number, T lymphocytes from AIDS patients have functional defects in both early *and* late stages of maturation. In that *in vivo* administration of IL-2 has no effect on transferrin receptor expression or T cell proliferation, and only partially restores T cell proliferation when added *in vitro*, it would appear that there may be an extrinsic factor *in vivo* which suppresses late stages of T cell activation. Further, although early stages of activation such as IL-2 production and IL-2R expression may be limited by an intrinsic defect of the infected T cell, it is possible that an extrinsic factor abrogates these as well.

Monocyte/macrophage and NK cell defects

The defects in T cell activation and elaboration of lymphokines (IL-2 and IFN-γ), and the resultant reduction in T cell proliferation may secondarily limit dependent effector mechanisms, including monocyte/macrophage and natural kill cell activity. In normal individuals, IFN-γ activates macrophages to kill microbial or tumor targets (50, 51). AIDS patients are seen to have diminished monocyte chemotaxis (52), and monocyte/macrophage killing of tumor targets (53, 54). Exogenous IFN-γ can restore killing of both tumor (53) and microbial (37) targets by monocyte/macrophages from these patients. IFN-γ augments the expression of class II major histocompatability complex (MHC) antigens on normal monocyte/macrophages (55). Not surprisingly, class II MHC expression is decreased on the monocyte/macrophage from AIDS patients, and can be restored to near normal levels by IFN-γ treatment *in vitro* (56). Interaction of helper T cells with antigen-presenting cells (APC), such as the monocyte/macrophage, is an MHC-II restricted process. Defects in helper T cell function then, may also reflect primary defects in the APC.

AIDS patients have decreased natural killer (NK) activity (43, 47). IL-2 (46, 57, 58) and IFN-γ (46, 59) enhance NK activity in both normal and AIDS patients, and do so via independent mechanisms (60). It is worth noting that NK activity appears to be important in the destruction of HIV-infected target cells (61), and interferon-γ suppresses the replication of HIV *in vitro* (62). Given the deficits in T cell activation and IL-2/IFN-γ production, the observed correlation between decreased interferon-γ production and the progression of disease from ARC to AIDS (45), and the deficits in IL-2/IFN-γ dependent effector functions, the question then remains, what is it that disrupts effective T cell

activation, lymphokine production and proliferation?

A soluble suppressor

Several studies have demonstrated circulating factor(s) in the serum of AIDS patients which can suppress T cell activation and proliferation (63–67). This factor(s) suppresses mitogen-induced IL-2 production and IL-2R expression (63, 65) by normal lymphocytes, proliferation of IL-2 dependent cytotoxic T cell lines in response to IL-2 (63, 64), and proliferation of normal lymphocytes in response to mitogens, soluble antigens, or alloantigens in the mixed lymphocyte reaction (MLR) (65, 67). The factor has the following characteristics (66): not lymphotoxic, stable @ pH 3–10 and up to, 60°C, inactivated @ 100°C, not ether extractable, not interferon, cortisol, IgG, IgM or an immune complex, not mediated by radiosensitive or T8 antigen-bearing suppressor cells, or increased prostaglandin E or decreased IL-1 production, does not reflect absence of a stimulatory or nutritive factor, inactivation of IL-2, inhibition of the IL-2 assay, or increased IL-2 turnover.

The suppressive effects of AIDS sera on normal lymphocytes persists after the cells have been washed, suggesting that the factor may be able to bind to receptors on lymphocytes (66). Pretreatment of IL-2R+ lymphoblasts with AIDS serum does not block binding of anti-IL-2R monoclonal antibodies (63), so the suppressor apparently does not act by blocking the IL-2 receptor. Further, gel filtration of serum from AIDS patients shows that the inhibitory activity coelutes with the immunoglobulin fraction (63). Immunoglobulins have molecular weights ranging from 150 000 daltons for IgG to 950 000 daltons for IgM. Ferritin has a molecular weight of approximately 460 000 dalton, and thus would be expected to coelute with the immunoglobulin fraction. It is proposed here that ferritin may be the circulating inhibitor.

Ferritin as the suppressor?

Several observations suggest that ferritin, particularly at the levels seen in AIDS patients, may be capable of suppressing T lymphocyte function. Ferritin suppresses mitogen-induced T lymphocyte blastogenesis (68–70). Although not examined specifically in T lymphocytes, ferritin and transferrin appear to utilize a common receptor-mediated endocytosis pathway in reticulocytes (71), and ferritin can disrupt transferrin endocytosis and reduce intracellular iron accumulation (72). As noted above, expression of the transferrin receptor (18) and interaction of transferrin with this receptor (18, 25) are required events in the activation and proliferation of T cells. In fact, monoclonal antibodies directed against the transferrin receptor have been shown to inhibit mitogen-induced proliferation (73), the MLR (30), and the generation of cytotoxic T cells (30).

By abrogating the receptor-mediated endocytosis of transferrin by T lymphocytes, ferritin may disrupt late stages of T cell activation, and by limiting T cell proliferation, the overall production of IL-2 and IFN-γ may be reduced.

Conclusion

As noted above, one study has demonstrated elevated serum ferritin levels in a small sample of AIDS and ARC patients (6). Several considerations, however, should be noted regarding this study. Ferritin may be nonspecifically elevated in inflammatory conditions (74), and various malignancies (1–4). The above study, however, uses only healthy heterosexuals as controls. More meaningful conclusions might be drawn if ferritin levels were also compared to those from patients with other conditions where ferritin is known to be elevated. Further, a mean serum ferritin for healthy heterosexual controls is reported as 160 μg/dl (i.e., 16 000 ng/ml), while most acknowledge the "normal" range to be 0–250 ng/ml (75). Given the extremely high values reported for normal controls, and the need for additional controls for comparison, it would be useful to more extensively explore the significance of elevated serum ferritin levels in AIDS patients. Preliminary examination here in 6 patients with CDC-defined AIDS has revealed a mean serum ferritin of 5 028 ng/ml (R 2,072–12,174 ng/ml).

No substantial proposal has been made regarding the significance of elevated ferritin levels in the pathogenesis of AIDS. It is proposed here that ferritin may disrupt functional processing of the transferrin (Tf) Tf-receptor complex and in so doing, limit T cell activation and proliferation. By limiting T cell proliferation, ferritin may indirectly cause reduction in the total lymphokine output of a given population of lymphocytes, and abrogate lymphokine-dependent immune function. Ferritin might directly limit IL-2 and IFN-γ production

as well. It would be useful to directly examine the impact of ferritin, at concentrations such as those seen in AIDS patients, on the processing of transferrin and production of IL-2 and IFN-γ by T lymphocytes. These studies are now in progress.

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