Lymphokines, Homeostasis, and Carcinogenesis

Guest Editorial

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Lymphokines are lymphocyte glycoproteins possessing typical hormone activities—secretion by one cell, specific interaction with another target cell, and physiologic regulation under feedback control of specific vital function (12, 13). Some common lymphokines are LAF, lymphotoxin, MMIF or MAF, TCGF, and leukocyte or α-IFN and immune or γ-IFN (table 1). Lymphokines are often leukocytotropic in their target cell direction and immunoregulatory in their action. Interleukocyte secretory-regulatory activities were first recognized in 1966 (14, 15), and some immunoregulatory lymphokines have been subclassified as interleukins (16, 17). LAF, for example, is mitogenic for and stimulates T-lymphocytes to secrete TCGF (18) and has been termed IL-1. TCGF or IL-2 promotes the continued replication of T-lymphocytes (19). IFN, although not formally labeled as an interleukin, directly stimulates NK cell activity (20) and thus has interleukin-like properties. As the actions of other lymphokines continue to be defined, many and possibly all will be shown to have interleukin-type activities.

The cytophilic behavior of lymphokines, although frequently lymphocytotropic, can be quite diverse, as evidenced by the ability of IL-1 to interact with fibroblasts and synovial cells (31, 45) and the ability of IFN and lymphokine to affect the growth and/or function of a variety of nonlymphoid normal cells and tumor cells (32). In addition to being secreted by lymphocytes, some lymphokines are released by nonlymphoid cells. For example, IL-1 is synthesized by keratinocytes (46) and IFN is produced by fibroblasts. Thus although lymphokines are primarily thought of as lymphocyte-derived immunoregulatory hormones, these cytotoxic bioactive glycoproteins can be secreted by cells other than lymphocytes with the hormonal action of lymphokines extending beyond the immune system.

Just as lymphokine secretion can be pluricellular in origin and lymphokine target direction can be pluricellular in origin, the regulatory actions of these glycoprotein hormones are pluripotent and multifaceted. Like most groups or classes of hormones, lymphokines display stimulatory, inhibitory, and antagonistic, opposing, or contravening actions. Lymphokine stimulation is exemplified by the induction of IL-2 secretion by IL-1 and T-cell proliferation by IL-2, as well as by the induction of an anticarcinogenic state in normal cells and enhancement of the sensitivity of tumor cells to NK cell destruction by lymphotoxin. Another example is the stimulation of NK activity by IFN. The suppression of macrophage migration by MMIF and the suppression of tumor cell growth by lymphotoxin are examples of lymphokine inhibitory actions. Less well appreciated but increasingly recognized and potentially of great physiologic importance are antagonistic or otherwise disparate lymphokine regulatory actions. The ability of IFN to inhibit tumor cell growth and viral carcinogenesis and yet to enhance X-irradiation carcinogenesis (21) is one example. Another example is the ability of lymphotoxin to inhibit ischemic or syngeneic...

Abbreviations used: IFN=interferon; IL-1=interleukin 1; IL-2=interleukin 2; LAF=lymphocyte-activating factor; MAF=macrophage activating factor; MMIF=macrophage migration inhibition factor; NK=natural killer; TCGF=T-cell growth factor.

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Editor's note: Periodically, the Journal publishes solicited guest editorials as a means of transmitting to investigators in cancer research the essence of current work in a special field of study. The Board of Editors welcomes suggestions for future editorials that succinctly summarize current work toward a clearly defined hypothesis regarding the cause or cure of cancer.
cinogenesis (52, 53) may be mediated in part through the initiation and progression of cancer. The ability of lymphoid cells and their products to participate in a variety of homeostatic responses has been recognized for many years [reviewed in (48)]. Recent observations suggest that the stimulatory and inhibitory actions and feedback-type regulation (58), which could limit the generation of effective lymphotoxin levels in an NK cell reaction, occurs later, 2-3 hours after exposure of target cells to IFN (56). A lymphotoxin-like soluble mediator has been identified in NK cell-mediated cytolysis (57), but it is not yet known whether during NK cytolysis lymphotoxin participates directly in the cytolytic destruction of the tumor target cell or enhances the sensitivity of the target cell to destruction, or both. Lymphotoxin secretion is also subject to feedback-type regulation (58), which could limit the generation of effective lymphotoxin levels in an NK cell reaction particularly if the target cells had been desensitized by IFN.

Lymphokine stimulatory and inhibitory actions and feedback regulation may also contribute to the lymphodependent phases of carcinogenesis (59) as lymphotoxin has shown to be one possible component in the bihapic inhibition of carcinogenesis by normal spleen lymphocytes (60). Lymphotoxin, moreover, can inhibit carcinogenesis at several points or stages. First, lymphotoxin can prevent the development of radiation carcinogenesis or chemical carci-

### Table 1.—Properties of some human immunoregulatory hormones

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Lymphotoxin</th>
<th>MMIF—MAF</th>
<th>IL-1—LAF</th>
<th>IL-2—TCGF</th>
<th>IFN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composition</td>
<td>Glycoprotein</td>
<td>Glycoprotein</td>
<td>Glycoprotein</td>
<td>Glycoprotein</td>
<td>Glycoproteins</td>
</tr>
<tr>
<td>Molecular weight</td>
<td>20,000-95,000</td>
<td>23,000-67,000</td>
<td>15,000</td>
<td>14,500-16,500</td>
<td>10,000-30,000</td>
</tr>
<tr>
<td>Isoelectric point</td>
<td>4.8-7.1</td>
<td>3.2-6.0</td>
<td>5.2-6.9</td>
<td>6.5-8.2</td>
<td>5.0-8.6</td>
</tr>
<tr>
<td>Cell source</td>
<td>T-lymphocyte</td>
<td>T- and B-lymphocytes</td>
<td>Monocytes, keratinocytes</td>
<td>T-lymphocyte</td>
<td>Varied</td>
</tr>
<tr>
<td>Stimulus for synthesis or release</td>
<td>Antigens, mitogens, proteases</td>
<td>Antigens, mitogens</td>
<td>MMIF, colony stimulating factor, lipopolysaccharide, others</td>
<td>IL-1</td>
<td>Varied</td>
</tr>
<tr>
<td>Target cells</td>
<td>Varied</td>
<td>Monocytes, macrophages</td>
<td>T-lymphocytes, synovial cells, fibroblasts</td>
<td>T-lymphocytes</td>
<td>Varied</td>
</tr>
<tr>
<td>Dominant or critical residue</td>
<td>β-D-Galactose</td>
<td>α-L-Fucose</td>
<td>&gt;1,000</td>
<td>1,000</td>
<td>&gt;3,000</td>
</tr>
<tr>
<td>Specific activity per μg protein</td>
<td>&gt;5,000</td>
<td>&gt;1,000</td>
<td>10^-10 M</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biological concentration/receptor-binding concentration</td>
<td>10-10 M</td>
<td></td>
<td>?/Dissociation constant=6 ppm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Under feedback regulatory control</td>
<td>Yes</td>
<td>Yes</td>
<td>?</td>
<td>Yes</td>
<td>?</td>
</tr>
<tr>
<td>No. of binding sites/target cell</td>
<td>?</td>
<td>?</td>
<td></td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>Unstimulated target cell</td>
<td>Yes</td>
<td>(1, 22-24, 47)</td>
<td>No</td>
<td>(18, 31, 33-37, 45)</td>
<td>No</td>
</tr>
<tr>
<td>Stimulated target cell</td>
<td>?</td>
<td>(6, 25-30)</td>
<td>No</td>
<td>(19, 38-44)</td>
<td>No</td>
</tr>
<tr>
<td>Species specificity</td>
<td>Yes</td>
<td>(20, 21, 32, 47, 49-51)</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>References</td>
<td></td>
<td></td>
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Lymphokines and Carcinogenesis

Lymphokines are natural and pharmacologically augmentable immunophysiological regulators. As such, they can be powerful positive or negative forces assisting or resisting and even defeating surgical, chemotherapeutic, radiotherapeutic, and combination modality intervention in the management of cancer. For example, the ability of lymphocytes to secrete lymphotoxin can remain depressed for years after therapy for Wilms' tumor (70), and whether the deficiency is congenital, acquired, or iatrogenic, it has the potential to affect the control and eradication of the primary tumor as well as prevention of subsequent carcinogenesis. Little is yet known about the normal range of lymphokine secretion and activity. It is important that we commence assessment of lymphokine secretion and function in normal healthy individuals as well as in individuals considered to be at increased risk for carcinogenesis. Alone, each lymphokine may be insufficient and ineffective as a cancer preventive and/or therapeutic agent. In combination with other lymphokines and nonimmunologic hormones to result in either stimulation or inhibition of carcinogenesis remains to be defined, because the additive and synergistic stimulatory as well as contravening actions of lymphokines constitute an unexplored area of immunophysiology and immunopharmacology.

Three additional recent observations warrant further comment. Lymphotoxin can induce or stimulate IFN secretion (67) and thereby through the secreted IFN indirectly stimulate NK cell activity. This mechanism of NK cell stimulation in conjunction with lymphotoxin-induced increased target cell sensitivity to NK cells would amplify the net target cell destruction. This is one example of the complex synergistic potential anticarcinogenic activities of the lymphokines. Interactions with other hormones are also possible. Two examples are the following: a) hydrocortisone has been shown to directly inhibit carcinogenesis at the level of the target cell (68) and to inhibit lymphokine secretion (69), and b) insulin recently has been found to negate the growth inhibitory action of lymphotoxin in insulin-responsive tumor cells (Greiner JW, Ransom JH, Evans CH: Unpublished observations). The potential, therefore, exists for combinations of IFN, lymphotoxin, hydrocortisone, and insulin as well other lymphokines and nonimmunologic hormones to result in either stimulation or inhibition of carcinogenesis. The extent to which lymphokines actually regulate carcinogenesis remains to be defined, because the additive and synergistic stimulatory as well as contravening actions of lymphokines constitute an unexplored area of immunophysiology and immunopharmacology.

Lymphokines are natural and pharmacologically augmentable immunophysiological regulators. As such, they can be powerful positive or negative forces assisting or resisting and even defeating surgical, chemotherapeutic, radiotherapeutic, and combination modality intervention in the management of cancer. For example, the ability of lymphocytes to secrete lymphotoxin can remain depressed for years after therapy for Wilms' tumor (70), and whether the deficiency is congenital, acquired, or iatrogenic, it has the potential to affect the control and eradication of the primary tumor as well as prevention of subsequent carcinogenesis. Little is yet known about the normal range of lymphokine secretion and activity. It is important that we commence assessment of lymphokine secretion and function in normal healthy individuals as well as in individuals considered to be at increased risk for carcinogenesis. Alone, each lymphokine may be insufficient and ineffective as a cancer preventive and/or therapeutic agent. In combination with other lymphokines and nonimmunologic hormones, lymphokines offer an adjunct to preventive, diagnostic, and therapeutic modalities of potentially the same powerful force previously

to toxicity (54). Down-regulation may be one means by which the host or developing cancer cell can circumvent and escape inherent homeostatic mechanisms for the prevention and control of cancer. Definition of the full spectrum of lymphotoxin actions and their in vivo physiologic significance should now be possible with the increasing availability of homogeneous preparations of lymphotoxin as well as other lymphokines together with their respective specific inhibitors and antibodies. Elucidation of the mechanisms by which the lymphokines individually and collectively maintain homeostasis is necessary to select the lymphokine activities that warrant monitoring in individuals at increased risk of carcinogenesis and to provide a more mechanistic rationale for the administration or manipulation of lymphokines in the interventive prevention and control of carcinogenesis.

Net effect on carcinogenesis?
1. null
2. prevention
3. enhancement
4. suppression
5. inhibition
6. reversal

**Text-Figure 1.**—Pathways of potential lymphotoxin and IFN stimulatory and inhibitory actions in natural lymphoid cell-mediated prevention, control, and eradication of carcinogenesis. Lymphotoxin and IFN can originate intrinsically and/or extrinsically in relation to the reaction of effector and target cells.

nogenesis by a not yet defined noncytotoxic mechanism (3) that is accompanied by a transient increase in high-molecular-weight cell membrane glycoprotein synthesis (61, 62). After carcinogen exposure, lymphotoxin can also irreversibly inhibit the further development of initiated and phorbol diester-promoted transformation (63). Inhibition of promoted transformation may occur by inhibition of the further progression of initiated cells as well as possibly by steric hindrance of the promoting action of the phorbol diester (64). Subsequent stages in carcinogenesis are susceptible to the various cytotoxic or cyto­reductive actions of lymphotoxin. The ability of the lymphokine to enhance the sensitivity of preneoplastic as well as tumor cells to NK destruction has been described above. Tumor cells are also susceptible to the growth-inhibitory and to a lesser degree to the cytolytic activities of the hormone (65). Susceptibility to lymphotoxin cytotoxicity, furthermore, can develop as either a transient or a permanent alteration during the preneoplastic stages but is present as a permanent genotypic alteration once expressed during the neoplastic stages of carcinogenesis (5, 66).

Lymphokinin, therefore, has the potential to alter the development of cancer through several diverse mechanisms. The net result can be prevention or inhibition of carcinogenesis. Alternatively, stimulation of carcinogenesis is possible should the hormone be down-regulated or otherwise inhibited during modulation of natural lymphoid cell cytothe hormone be down-regulated or otherwise inhibited during modulation of natural lymphoid cell cytoxic activities of the hormone (65). Susceptibility to the growth-inhibitory and to a lesser degree to the cytolytic activities of the hormone (65). Susceptibility to lymphotoxin cytotoxicity, furthermore, can develop as either a transient or a permanent alteration during the preneoplastic stages but is present as a permanent genotypic alteration once expressed during the neoplastic stages of carcinogenesis (5, 66).
demonstrated for androgens, estrogens, glucocorticoids, and other hormones in the prevention, control, and eradication of cancer.

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