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Leukemia Inhibitory Factor: A Biological Perspective

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Abstract The notion that a single hormone may exert a broad range of effects has become well established. As such, leukemia inhibitory factor (LIF) is a prime example. LIF was initially described, purified, and genetically cloned on the basis of its ability to induce the differentiation and suppress the clonogenicity of the monocytic leukemia cell line, M1. Subsequently, it has become apparent that in vitro LIF inhibits the differentiation of pluripotential ES cells, stimulates the synthesis of hepatic acute-phase proteins, induces a switch in neurotransmitter phenotype from adrenergic to cholinergic, suppresses adipocyte lipoprotein lipase activity, and results in an increase in bone resorption. Moreover, elevation of LIF levels in vivo has a number of patho-physiological consequences, many of which parallel those effects observed in vitro. The challenge that lies ahead is to determine whether other sites of LIF action exist and to define more clearly the physiological role LIF plays in vivo.

A major mechanism of cell-cell communication is by the production and secretion of polypeptide hormones by one cell type, which act either systemically or locally, via interaction with specific receptors on the surface of responsive cells. Recently, it has become apparent that hormones initially described and named, on the basis of a specific action, in many cases exert a spectrum of effects on a broad range of cell types. Moreover, the effects exerted are often mimicked closely by other hormones. Hormones that act in a pleiotropic manner are, for example, transforming growth factor-β (TGF-β), the various fibroblast growth factors (FGFs), interleukin-6 (IL-6), and leukemia inhibitory factor (LIF). This review will focus on the various biological effects ascribed to LIF.

Key words: hemopoiesis, ES cells, myoblasts, osteoblasts, hepatocytes, neurones

IN VITRO ACTIONS OF LIF

Actions of LIF on Haemopoietic Cells

LIF was initially described and purified on the basis of its ability to induce the differentiation and suppress the clonogenicity of the murine monocytic leukemia cell line, M1 [1–4]. The amino acid sequence of LIF purified from Krebs II ascites tumor cell conditioned medium was found to be novel [5], being unrelated to several other molecules displaying similar actions on leukemic cells, such as granulocyte colony stimulating factor (G-CSF), IL-6, and IL-1 [6–9]. More importantly, amino acid sequence enabled genomic and cDNA clones encoding murine and human LIF to be isolated [10,11] and large (mg) quantities of recombinant LIF to be produced in bacteria, yeast, and mammalian cells and purified to homogeneity [10–12; Willson et al., in preparation; Hilton et al., in preparation].

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In addition to its ability to induce the differentiation of M1 cells, LIF is capable of synergizing with GM-CSF in the induction of HL-60 differentiation and G-CSF in the induction of U937 differentiation [13]. More recently, LIF has been found to support the the proliferation of a factor-dependent myeloid cell line, DA-1a [14], a function shared with IL-3 and GM-CSF. Likewise, LIF is weakly mitogenic for a number of cell lines derived by transfection of murine fetal liver cells with a retrovirus harbouring an activated myc gene and can potentiate the mitogenicity of IL-3 and erythropoietin [Cory, Maekawa, McNeil, and Metcalf, submitted].

The action of LIF on normal hemopoietic cells has been more difficult to define. When used alone, LIF does not stimulate the formation of colonies of any lineage in cultures containing bone marrow or fetal liver cells. Neither, with a recently noted exception, does LIF modify the number, type, or size of bone marrow colonies or clusters stimulated by interleukin-3 (IL-3), granulocyte-macrophage-CSF (GM-CSF), macrophage-CSF (M-CSF), or G-CSF [8,9]. However, like IL-6 [15], G-CSF [16], and possibly erythropoietin [17,18], LIF has been found to enhance

the production of megakaryocyte colonies stimulated by IL-3 [Metcalf et al., submitted]. In addition, elevated levels of LIF in mice result in increased megakaryocyte progenitor, megakaryocyte, and platelet numbers [19]. LIF has also been reported to promote the entry of hemopoietic stem cells (blast-CFC) into cell cycle and thereby increase responsiveness of those cells to IL-3 [20]. Again, IL-6 and G-CSF also exhibit this capacity [21]. This effect of LIF on hemopoietic stem cells may also explain the observation that LIF increases the frequency of retroviral infection of these cells [22].

LIF and ES Cells

It is perhaps outside the hemopoietic system that LIF exhibits its most interesting effects (Table I). During 1988, it was realized that LIF displayed a number of properties that were similar to a molecule termed differentiation-inhibitory activity (DIA) [23,24]. In contrast to the action of LIF on M1 cells, DIA suppresses the differentiation and thereby maintains the pluripotentiality of embryonal stem cells. LIF receptors, with a comparable specificity and affinity as those on M1 cells, were found to be expressed by all ES cell lines and embryonal carcinoma (EC) cell lines tested [24]. Purified recombinant LIF was found to substitute completely for crude sources of DIA, whether provided in the form of a feeder layer or conditioned medium, in the inhibition of ES cell differentiation, in vitro [24]. Importantly, it has been possible to establish karyotypically normal ES cell lines by the culture of inner cell mass (ICM) cells in LIF. When maintained exclusively in LIF, for up to 20–30 passages, these cell lines retain the ability to contribute to the formation of all tissues, including the germ line, upon injection into recipient blastocysts [25].

TABLE I. LIF and Its Synonyms*

Name	Defining action	Reference
LIF	Induction of M1 differentiation	3,4,10,11
D-Factor	Induction of M1 differentiation	1,2,27
DIF	Induction of M1 differentiation	57
DIA	Inhibition of ES cell differentiation	23
DRF	Inhibition of ES cell differentiation	58
HSF-II and III	Stimulation of acute phase protein synthesis	33,34
CNDF	Induction of cholinergic neuronal differentiation	40,41
HILDA	Stimulation of DA-la proliferation	14
MLPLI	Inhibition of lipoprotein lipase activity	45
OAF	Stimulation of bone resorption in vitro	26

*Abbreviations used: CNDF, cholinergic neuronal differentiation factor; D-Factor, differentiation-inducing factor (DIF); DIA, differentiation inhibitory activity; DRF, differentiation-retarding factor; HILDA, human interleukin for DA-1a cells; HSF, hepatocyte-stimulating factor; LIF, leukaemia inhibitory factor; MLPLI, melanocyte-derived lipoprotein lipase inhibitor; OAF, osteoclast-activating factor.

LIF and Bone Metabolism

In 1986 Abe et al. [26] demonstrated that spleen conditioned medium contained factors that could induce M1 cell differentiation and stimulate bone resorption in vitro. It was shown that that the two activities resided in a single basic molecule with an apparent molecular weight of 67,000, that has subsequently been shown to be identical to LIF [27]. Stimulation of bone resorption in vitro has been confirmed using purified recombinant LIF and shown to be indomethacin sensitive, suggesting that the effect on osteoclasts is mediated indirectly by prostaglandin synthesis, perhaps by osteoblasts [28]. In support of this conclusion, a number of effects of LIF upon the anabolic processes of primary osteoblasts and osteoblastic cell lines have been noted [28,29] and indeed osteoblasts, which are usually present in bone cultures, express specific, high affinity receptors for LIF, whereas osteoclasts do not [29].

LIF and the Acute Phase Response

A great deal of interest has been focussed on a set of molecules identified on the basis of an ability to enhance the synthesis of acute phase proteins by the human hepatic cell line Hep-G2. Biochemical fractionation of one source of these activities (medium conditioned by the human colonic carcinoma cell line COLO-16) led to the purification of three separate glycoproteins, termed hepatocyte-stimulating factors (HSF) I, II, and III [30]. HSF-I was shown to be identical to IL-6 [31], while HSF-II and III were found to be distinct from HSF-I, but share with each other a number of biochemical and biological

properties [32]. Subsequently, HSF-III was found by functional, biochemical, antigenic, and receptor binding criteria to be distinct from IL-6 [33], but indistinguishable from LIF [34]. The presence of specific, high affinity receptors for LIF on primary foetal and adult parenchymal hepatocytes [35], as well as the hepatic cell line Hep-G2 [D.J. Hilton, unpublished observation] and the demonstration that, like IL-6, LIF concentrations in the serum rise after injection of mice with endotoxin [9], supports the notion that LIF may play a physiological role in hepatic function in response to tissue damage or infection.

Neurotransmitter Phenotype and the Effects of LIF

It has been realized from both in vitro [36] and in vivo [37] experiments that the neurotransmitter synthesized by a cell is by no means fixed, but varies with environment. Notably, if noradrenergic sympathetic neurones, or sensory and spinal cord neurones are cultured with medium conditioned by the myoblastic cell line L6, or by primary heart cells, a switch to a cholinergic phenotype is observed [36,38,39]. Fractionation of medium conditioned by newborn rat heart cells resulted in the purification of the active factor [40], which was termed cholinergic neuronal differentiation factor (CNDF). Like LIF, CNDF was shown to be basic and glycosylated on at least 6 asparagine residues [40]. The identity of LIF and CNDF was confirmed by amino acid sequence analysis of the latter and the demonstration that purified recombinant LIF could duplicate the action of CNDF in cultures of sympathetic neurones [41].

LIF and Myoblast Proliferation

In vitro, myoblasts proliferate slowly and readily differentiate and fuse to form muscle fibers. It has been demonstrated that addition of low concentrations of LIF to cultures of primary human and murine myoblasts markedly stimulates cell division [42; Austin et al., in preparation]. The direct nature of the action of LIF on these cells is suggested by the presence of specific receptors for LIF [Nicola et al., unpublished observation]. Given the ability to transplant cultured myoblasts into animals with genetic muscular defects [43] and the potential to use such an approach to treat human myopathies [44], the capacity to stimulate the proliferation of myoblasts in vitro and therefore obtain enough cells for large scale transplantation is clearly important.

LIF, Lipoprotein Lipase, and Cachexia

Recently Mori et al. [45] investigated the mechanism by which a cell line, SEKI, established from a human melanoma, caused cachexia upon injection into nude mice. They noted that medium conditioned by SEKI cells was a potent inhibitor of lipoprotein lipase activity in 3T3-L1 adipocytes. The active molecule was purified to homogeneity and shown by amino acid sequence analysis to be identical to LIF. Inhibition of lipoprotein lipase, which results in a reduction in the uptake of triacylglycerides into cells, has also been observed in response to the TNF-α, IFN-γ, and IL-1 [46–48]. In turn, this has been postulated as one possible cause of cachexia in vivo. Interestingly however, neither TNF-α, TNF-β, nor IL-1 has been shown to be produced by tumor cells that induce cachexia, but rather is made by host cells in response to tumors. In this context, it may be that aberrant LIF production by some tumours is of importance in the etiology of cachexia.

ACTIONS OF LIF IN VIVO

It has long been realized that actions of regulators defined in vitro must be correlated with effects in vivo [49]. Toward this end, most recent in vivo studies of cytokine function have centered on the effect of an elevation of regulator levels. Two experimental routes have been utilized to elevate LIF levels in mice. The first involved engraftment of mice with non-leukemic hemopoietic cells, FDC-P1 cells, that had been engineered to constitutively produce high levels of LIF by introduction of LIF-expressing retroviral construct [50,51]. The second approach involved repeated intraperitoneal injection of purified recombinant LIF [19].

In both experimental situations complex pathologies were observed, in which several effects correlated well with the known action of LIF in vitro. Strikingly, a few days after engraftment with LIF-producing FDC-P1 cells or the commencement of injection of LIF, a marked reduction in the body weight of mice was observed, the cause of which appeared to be an almost complete loss of subcutaneous and abdominal fat. Such an effect may reflect the ability of LIF to inhibit lipoprotein lipase activity and therefore fatty acid uptake in adipocytes in vitro, and reinforces the possibility that LIF may be respon-

sible in part for cachexia in humans. The other effects of LIF, common to both in vivo systems, were the presence of ruffled fur and irritable behaviour, classic signs of an acute phase response, such as an increase in erythrocyte sedimentation rate and a fall in albumin levels, an increase in megakaryocyte progenitor, megakaryocyte, and platelet levels, and dysregulated calcium metabolism. This was accompanied, in the engrafted model, by a marked increase in the deposition of new bone, to the extent that medullary hemopoiesis was severely limited and compensatory splenic and hepatic hemopoiesis was observed. Again, such actions may represent the in vivo correlates of effects observed with LIF in vitro (Table II).

The major differences between the two modes of elevating LIF levels in vivo centered on the state of the thymus, adrenals, pancreas, and gonads. In mice engrafted with LIF-producing FDC-P1 cells, the thymus was severely atrophied, the brown layer of the adrenal cortex and the acinar tissue of the pancreas had degenerated, and spermatogenesis and production of corpora lutea was dysregulated. In mice that had been injected with the highest dose of LIF (2 μg, three times daily), thymus atrophy was observed, but other degenerative effects were absent. However when injected with a lower dose of LIF (200 ng, three times daily) although an increase in megakaryocyte and platelet numbers was still evident thymus atrophy was not.

TABLE II. In Vitro Actions of LIF and Possible In Vivo Correlates

In vitro action	In vivo effect of elevated LIF levels	Reference
↑ acute phase protein synthesis	↑ erythrocyte sedimentation rate ↓ albumin concentration	19,33,34,50
↑ megakaryocyte colony formation	↑ megakaryocyte progenitor number ↑ megakaryocyte number ↑ platelet number	19,50
↓ lipoprotein lipase activity	↓ subcutaneous and abdominal fat → cachexia	19,45,50
↑ cholinergic neuronal differentiation	↑ nervousness	19,40,41,50
↓ bone resorption	↑ serum Ca^{++} levels ↑ Ca^{++} deposition in tissues ↑ bone deposition ↑ osteoblast number	19,26,50,51
↑ muscle proliferation	?	42
↓ ES cell differentiation	?	23–25

The experimental elevation of regulator levels in vivo, as described for LIF, allows correlations to be made with in vitro actions and also yields preliminary information that is useful for prospective clinical trials (e.g., concerning effective routes of administration and tolerable doses). It should be kept in mind, however, that such effects reflect the pathological response to excess LIF levels, rather than the physiological role of LIF. A complementary route of accruing information concerning the actions of cytokines is by ablating or disrupting the genes encoding them by homologous recombination [52]. As with elevation of regulator levels, such an approach may hint at the physiological roles of the regulator but the effect observed will, once again, be pathological. A greater limitation on such an approach may be encountered with genes that are important in early embryonic events, as has been suggested for LIF. It might be expected that interference with production of critical proteins during this period of development would result in early in utero death and thus mask any later phenotypic changes in mice.

FUTURE DIRECTIONS OF STUDY

The sites of LIF action have also begun to be explored by attempting to define those cell types that express receptors for LIF and those that produce LIF during development and in the adult. It has been possible, in vitro, to show that LIF receptors are expressed on cells of the monocyte [34] and megakaryocyte lineage (Metcalf et al., in preparation), with expression increasing with differentiation. Receptors are also found on osteoblasts but not osteoclasts [29], fetal and adult parenchymal hepatocytes [53], EC and ES cells, and presumably cells of the ICM of the blastocysts.

In cases such as ES cells, hepatocytes, osteoblasts, and megakaryocytes, LIF receptor expression correlates well with the ability of cells to respond to LIF. The binding of LIF to macrophages raises the possibility that LIF may also

affect the production or function of these cells; however, to date no such function has been demonstrated. The results concerning LIF receptor distribution in vivo and during development are preliminary. It remains to be determined in detail where and when receptors are expressed during embryogenesis and, most particularly, at what stage of pre-implantation development LIF receptor expression begins.

Clearly, it is not enough to know those cell types that express a receptor for a given hormone—one must also determine whether the hormone is also present and, hence, at any given time whether a response may be elicited. To date the majority of data concerning the pattern of LIF expression have been restricted primarily to analyses of cell lines [see, for example, 1–4,10,11,14,23,24,26,29–32,40,41] which, while useful in defining sources from which native LIF may be produced and characterized, are of questionable worth when attempting to determine the types of primary cells that produce LIF.

Analysis of LIF production by primary tissues is critical. At this time, however, data is preliminary. Although tissues removed from untreated mice contain extremely low or undetectable amounts of LIF mRNA, as judged by the very sensitive polymerase chain reaction procedures, in mice injected with endotoxin, LIF mRNA was readily detectable in several tissues, for example the lung and brain [M.A. Brown and N.M. Gough, unpublished data]. Using blastocysts grown in vitro from single cell embryos, mRNA encoding LIF and IL-6 but not IL-3 or GM-CSF were detected by polymerase chain reaction [54]. The capacity of medium conditioned by blastocysts to support the proliferation of the plasmacytoma KD83 and the myeloid cell line DA-1a also suggested that the factors themselves are secreted, although whether by trophoblasts or cells of ICM was not investigated. It is not, as yet, clear at what stage during early embryogenesis LIF might act. Several possibilities, however, suggest themselves, notably, given the presence of specific receptors for LIF on trophoblasts [Hilton et al., in preparation], the process of implantation of the embryo in the uterine wall. It is perhaps noteworthy that granular cells of the metrial gland, which forms in the uterine wall at the site and time of implantation, consistently express LIF mRNA and protein [55]. A second possible period of LIF action, given the presumed expression of LIF receptors by cells of the ICM, is gastrulation, in which cells of the inner cell mass differentiate into the primary germ layers, the endoderm and the ectoderm.

Rat embryonic heart cells have also been shown to produce LIF in vitro [40]. A possible role for such production is that LIF may act as a neurotrophic factor, promoting survival of those neurones that innervate the developing heart. It will be important to determine whether other structures that are heavily innervated also produce LIF at the appropriate time. Consistent with a neural site of LIF action was the demonstration that astocytes express mRNA for LIF when stimulated with endotoxin in vitro [56]. The next phase of such work requires that a more precise localisation of LIF producing and LIF responsive cells be made. As such, systems that enable the binding of ^{125}I-LIF to tissue sections to be analysed by autoradiography, LIF protein to be detected immunohistochemically, and LIF mRNA to be visualised by in situ hybridization will be invaluable.

CONCLUDING REMARKS

The picture of LIF that has been built up over the past five years is one of a hormone that elicits a bewildering range of effects in vitro. That some of these effects are observed in vivo is reassuring, although an understanding of the physiological roles of LIF is a goal that remains somewhat distant. Progression toward this target will be aided by further experimentation in vitro, by the generation of mice that lack a functional gene for LIF via homologous recombination, and ultimately through a detailed knowledge of the pattern of expression of LIF and its receptor in vivo and the circumstances that lead to an alteration in its expression.

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