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A role for growth hormone and prolactin in leukaemia and lymphoma?

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Abstract. Growth hormone (GH) and prolactin (PRL) qualify as lymphohaemopoietic growth and differentiation factors, and so does insulin-like growth factor (IGF)-I, which mediates many of GH activities. Although there is only limited evidence that endocrine, paracrine or autocrine GH or PRL play a role in human leukaemia and lymphoma, the expression of these factors or their receptors may have diagnostic or therapeutic implications. Indeed, the participation of GH, PRL or IGF-I in the development or progression of certain haematological malignancies or to the antitumour immune response has been documented. Examples discussed in this review include a rat lymphoma in which the PRL receptor acts as an oncogene; the rat Nb2 lymphoma, which is dependent on PRL for growth; and experiments showing that PRL stimulates natural killer cell activity and the development of lymphokine-activated killer cells.

Key words. Growth hormone; prolactin; insulin-like growth factor; leukaemia; lymphoma; second messenger; JAK; STAT.

Introduction

Growth hormone (GH) and prolactin (PRL) promote normal haemopoiesis, play a direct role in the growth and function of leukocytes and participate in host defence against infections and tumours through endocrine or paracrine/autocrine mechanisms (reviewed in the present issue and in refs 1–5). The possible contribution of these hormones to the development and progression of leukaemia and lymphoma should therefore also be considered. An indirect role for GH, mediated through insulin-like growth factor-I (IGF-I), is also plausible. Indeed, IGF-I qualifies both as a growth and a differentiation factor for haemopoietic and lymphoid cells and as a growth factor for many types of tumour cells [1–5 and papers by van Buul-Offers and Kooijman and by Foster et al. in this issue]. In the present review, we will first address the possible role of GH, PRL and IGF-I in leukaemo- and lymphomagenesis, the expression of these factors in leukaemic tissues (by tumour or by stromal cells) and the expression of receptors for GH, PRL or IGF-I on leukaemic cells. We will next summarize the evidence for effects of these factors in the progression and regression of leukaemia and lymphoma.

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Leukaemogenesis

Clinical context

Clinical data on a possible role for PRL, GH or IGF-I are limited. In acromegalic patients, the incidence of polyposis and carcinoma of the colon is increased [6]. There are occasional reports of leukaemia development during the course of acromegaly [7], but there is no evidence that the incidence of leukaemia is increased in this disease. There has also been speculation that the hormones of pregnancy play a role in cancer development or progression. Hodgkin's and high-grade lymphoblastic lymphomas are among the most frequent malignancies associated with pregnancy. For both diseases, clinical relapse or status quo is common during pregnancy. Marked aggravation of non-Hodgkin's lymphoma is frequent post-partum, and breast feeding has been mentioned as a contributory factor, pointing to a possible role for PRL [8]. A critical issue was a suggested increase in leukaemia incidence among patients treated with GH.

GH is not leukaemogenic

GH has been widely used in children with short stature, with or without GH deficiency. Some athletes also use it to enhance performance. In 1992, more than 30 cases of leukaemia had been reported during or after treatment with GH [9]. Consistent with these findings, prior hypophysectomy prevented the induction of leukaemia by murine leukaemia virus (MuLV) in mice [10], and it was suggested that deprivation of GH was the critical factor. In children receiving GH, a careful review indicated that in half of the cases presenting with leukaemia, preleukaemic states or other conditions favouring the appearance of leukaemia (such as Fanconi's anaemia or prior radiotherapy or chemotherapy) were present [11, 12]. Today, there are no indications that GH favours the development of leukaemia in patients who have no predisposing factor. Numbers are too small to establish whether GH stimulates the development of leukaemia in predisposed children. The point here, however, is that GH is not leukaemogenic in children (with the possible exception of a cohort of Japanese children), although it has been found to be clastogenic in some studies (but not in others) in human or animal cells [13–15]. Nevertheless, careful monitoring of patients receiving GH is recommended, as GH and IGF-I can stimulate the growth of normal and transformed leukocytes [4, 16, 17, 19 and see below]. Lymphoma has also been reported in GH users, but there has been no recent evaluation of incidence [18].

Constitutive activation of hormone receptors

In a single rat, MuLV insertion resulted in transcriptional activation of the PRL receptor (PRL-R) and lymphoma development in the thymus [20]. The PRL-R can thus behave as an oncogene. The IGF-I-R often plays a critical role in the maintenance of the transformed phenotype in several types of tumours [13], including some haematological malignancies. For instance, transfection with the IGF-I-R relieved cells from interleukin (IL)-3 dependency [21]. Similar results were also obtained through transfection with the GH-R [22 and M.-C. Postel-Vinay, personal communication].

Constitutive activation of signalling pathways

GH and PRL utilize the Janus kinase (JAK)-signal transducers and activators of transcription (STAT) pathway for signalling, which modulates cell growth and differentiation (reviewed in this issue by Yu-Lee et al.; see also refs 23–25). Neoplastic transformation can be related to constitutive activation of receptors for growth factors but also to constitutive activation of signalling molecules. For instance, gain-of-function mutations of the *Drosophila* JAK-2 homologue encoded by the *hopskotch* gene result in neoplasia of the larval lymph glands [26]. In man, B lineage acute lymphoblastic leukaemia cells from patients in relapse have constitutively activated JAK-2 (a protein kinase normally activated e.g. by the GH- or the PRL-R), and a specific JAK-2 inhibitor was found to block leukaemic cell growth in vitro and in vivo [27]. A recent report identifies the protein tyrosine kinase domain of JAK-2 as a fusion partner for *Tel* (the ETS-variant gene 6) as a result of translocation, in one acute B cell lymphoid leukaemia in a child and in one atypical chronic myelogenous leukaemia [28, 29]. Constitutively activated STAT-5 (a JAK-2 substrate normally phosphorylated in response to e.g. GH and PRL) has been found in freshly explanted myeloid and lymphoid leukaemic blasts and in Bcr-Abl-expressing cell lines [30–33].

Production of GH, PRL or IGF-I by leukaemia cells

Normal leukocytes and bone marrow stromal cells express variable levels of PRL, GH and IGF-I, depending on the differentiation and activation stage [3]. Expression of GH or PRL has also been unequivocally demonstrated in several transformed haemopoietic cell lines. The clinical relevance of the latter data is questionable, as hormone production was sometimes found in subclones only and was most probably not present in vivo. Hormone expression is often very low and only in a few cases has an autocrine effect been observed.

Myeloid leukaemia

Scarce data exist regarding the production of PRL by myeloid leukaemia cells. A moderate increase in serum

PRL levels has been reported in 16 patients with acute myeloid leukaemia (AML) (out of 28) in one series. Only in one of these cases was the presence of PRL in leukaemic blasts investigated and found positive [34]. In addition to the 23-kDa PRL, immunoreactive bands at 43 kDa (dimer?) and at 16 kDa were identified by Western blotting, although no demonstration of active synthesis or PRL gene activation was provided by those authors.

Lymphoid leukaemia

More data exist regarding the expression of PRL by transformed lymphoid cells. Several T cell lines and one natural killer (NK) cell line have been shown positive for both PRL messenger RNA (mRNA) and protein (glycosylated and nonglycosylated forms) [35–38 and L.M., unpublished data]. In contrast to the faint expression of PRL by B cells from peripheral blood, several B cell lines express PRL more vigorously. The first to be described was IM9-P, a clone derived from the IM9 Epstein-Barr virus-positive B lymphoblastoid cell line [39]. The IM9 line has lost the immunoglobulin synthetic activity and has acquired the ability to produce PRL. The two events are not correlated, since two clones were generated from this cell line: both were unable to produce immunoglobulin G, but one was a PRL producer (IM9-P3) and the other (IM9-P6) was not [40]. Studying a panel of 20 non-Hodgkin's lymphoma cell lines, we have found active synthesis of the two pituitary PRL forms by the parental cell line Ramos. With the exception of two, all the other cell lines expressed both PRL (23.5 and 25 kDa) and its mRNA (L.M., unpublished data). So far, only the serum-free Ramos Burkitt-derived line has been shown to produce GH [41]. Very recently, the presence of GH transcripts and immunoreactive GH was also demonstrated in the HL60 and K562 cell lines (R. Kooijman, unpublished results). The expression of IGF-I in leukaemic cells is more common than that of GH or PRL [2–4, 16, 42]. For all three hormones considered here, little is known about the control of expression. In particular, although many leukocytes express receptors for GH-releasing hormone or somatostatin, these factors do not seem to control GH expression in leukocytes. It is also not known to which extent IGF-I in tumour or stromal cells is dependent on (endocrine or paracrine) GH. Extrapituitary PRL expression is often initiated from the 'extrapituitary promoter', which is under a poorly understood control, different from the 'pituitary promoter'. Thus, PRL transcripts in leukocytes are about 150 bp longer than in the pituitary, due to an extra 5′-noncoding exon [5, 37, 43].

Leukaemic cells often express receptors for PRL, GH or IGF-I

Most types of normal leukocytes, endothelial or stromal cells express receptors for and respond to GH, PRL and IGF-I. The presence of receptors on the cell surface has also been demonstrated in many fresh samples of leukaemic cells and on cell lines [2–4, 77].

PRL-R

For studies in humans, it is important to note that primate GH also binds to the PRL-R. Most of the studies on the PRL-R were done, not on mammary cells – the obvious target – but on the rat Nb2 lymphoma cell line. The Nb2 PRL-R is a truncated form of the long form of the PRL-R. There is no evidence that the mutation contributed to the transformed phenotype [44]. The Nb2 cell line originally required lactogens (e.g. PRL, placental lactogens or primate GH) for growth, and this provided the basis for a sensitive bioassay. Lactogen-independent sublines were subsequently derived [45].

Using the monoclonal antibody PrR-7A, we have detected in the ^{35}S-labelled immunoprecipitate of $CD34^+$ human myeloid progenitors a 47-kDa protein which is much less than the expectyed 85 kDa. The most likely explanation is proteolysis. (So far, a short form of the PRL-R has been described in the rat but not in humans.) As both cell division and transcription of the erythropoietin-R gene are triggered by PRL in these cells, the presence of a long form (able to transduce signals) is postulated [46 and L.M., unpublished results]. Receptors for PRL were detected by the same antibody on primary AML blasts of the M4 type, and stimulation by either hPRL or recombinant hPRL increased both the DNA synthetic activity and the susceptibility of these cells to lymphokine-activated killer (LAK) activity [47]. Attempts to confirm these data with the promyelocytic HL60 cell line were unsuccessful (L.M., unpublished results). However, other authors have described increased DNA synthesis in these cells after PRL treatment [48], despite the reported absence of PRL binding [37, 49].

A high number of high-affinity PRL-Rs have been described on the Nb2 T lymphoma cell line by both binding of labelled lactogens and cytofluorometric analysis [50, 51]. Human T cell lines display a variable expression of PRL-R. Jurkat cells are strongly positive, while Molt-4 cells are negative. The PRL high-producer YT NK cell line does not express PRL-R [36, 37, 49, 52]. In a recent study we evaluated the expression of PRL-R on NHL cell lines. A wide range of expression from strongly positive (e.g. Daudi) to negative (the most common situation) was observed.

Except for Daudi, no correlation was found between PRL and PRL-R expression. In addition to the expected size, shorter forms (possibly degradation products) were always observed (L.M., unpublished results).

GH-R

The GH-R has been identified on fresh samples of leukaemia or lymphoma cells, on a limited number of leukaemia cell lines (K562, Molt4, REH) and on various lymphoblastoid cell lines (such as the IM-9 line) [11, 17, 53, 54].

IGF-I-R

The IGF-I-R has received much attention, in particular in multiple myeloma [2, 3, 16, 55]. For studies with IGF, it must be remembered that insulin and IGF-II also bind to the IGF-R type I (IGF-I-R).

Effects of GH, PRL or IGF-I on leukaemic cells

Isolated reports of leukaemic or lymphoma cells invading endocrine glands such as the pituitary suggest that hormones affect homing, growth or escape from immune surveillance [56–59]. In animal models, hypophysectomy has been shown to induce regression of one form of myeloid leukaemia [60]. In humans, isolated case reports may suggest that GH favoured disease progression, but this has never been unambiguously established [61]. In vitro studies with physiological or pharmacological concentrations have documented the growth-promoting effect of GH in several cell lines [11, 12, 17]. GH is an autocrine growth factor for the Ramos-sf line (derived from a Burkitt lymphoma), but this is probably a rare occurrence [41]. Similarly, PRL is an autocrine growth factor for the Jurkat T-cell leukaemia [36]. The rat Nb2 T cell lymphoma cell line requires PRL for growth, and PRL-induced gene expression has been studied in detail (ref. 62 and see L.-y. Yu-Lee et al., this issue). Altered expression of bcl-2 and bax are each associated with PRL-stimulated cell cycle progression in Nb2 cells [63, 64]. Some effects of GH have been studied in the IM-9 and K562 lines [65, 66]. In fresh leukaemia cells, physiological concentrations of GH increase the expression of GH-R [53]. A proliferative response was induced only in one immature T cell leukaemia, out of 19 primary leukaemias (AML and acute lymphoid leukaemia) tested [53]. Unexpectedly, the GH variant GH-V stimulates the proliferation of IM-9 cells better than the pituitary GH-N (O. Thellin, personal communication). IGF-I is a growth factor for many normal and neoplastic haemopoietic cells [67–74 and this issue, papers by Foster et al. and by van Buul-Offers and Kooijman]. IGF-I stimulates the growth of freshly isolated myeloid leukaemia cells and myeloid as well as erythroid cells and myeloma cells [16, 72–74]. Interestingly, IGF-I has been shown to stimulate the production of granulocyte-macrophage colony stimulating factor (GM-CSF) by some freshly explanted AML cells [74]. Increased growth of myeloma cells (but not of normal B cells) was seen with IGF-I alone or in combination with IL-6.

Effects of GH and PRL in the antitumour response

GH and PRL may not be major immunomodulatory factors in humans, but they undoubtedly play a role in the homeostasis of the immune system as shown by the decrease in NK cell numbers in GH-deficient children and in hyperprolactinaemic adults (see paper by Velkeniers et al. in the present issue).

Effects of GH and PRL may thus be both direct – at the level of the leukaemia cell – or indirect – at the level of the host response to leukaemia cell growth. For instance, GH and PRL modulate cytokine expression [75, 76 and R.H., unpublished results], with possible effects on leukaemia cells or on antitumour response. An interesting situation has been reported in a subset of patients with B cell chronic lymphocytic leukaemia: immunoglobulin-bound PRL (found in some serum samples) that has no lactogenic activity (in the Nb2 bioassay) was able to stimulate leukaemia cell growth [77]. Engagement of both the PRL-R and the receptor for the Fc portion of immunoglobulin (Fc-R) was required for this activity.

PRL has a protective effect against tumour growth, since lysis of tumour cell lines by NK-LAK cells is increased by near-physiological concentrations of the hormone [78]. In addition, the same concentrations of the hormone synergize with ineffective, low-dose IL-2 to induce LAK activity against primary leukaemia cells. These effects are apparently mediated through secretion of interferon-γ [79]. The individual and synergistic effect of PRL and IL-2 on NK cells may be explained by activation of convergent signalling pathways and transcription factors. One of these, IRF-I, is one of the early genes activated by PRL in Nb2 cells and is correlated with entry into the cell cycle. This transcription factor seems to be involved in the activation of perforin-dependent killing by NK cells, since mice lacking IRF-I are devoid of antitumour cytotoxic function [80].

Perspectives

1) Environmental, pharmacological or pathological disruption of the endocrine network may affect the

homoeostasis of the haemopoietic system and contribute to the development, progression or regression of haematological malignancies.

2) The expression of GH, PRL, IGF-I and the corresponding receptors on leukaemia/lymphoma cells may have diagnostic implications. For hormones and receptors, several variants and isoforms have been identified. Their relevance for tumour biology is illustrated by the fact that GH has angiogenic activity [81], and a 16-kDa PRL variant has antiangiogenic activity [82]. Different receptor isoforms can use different signalling pathways.
3) Whereas IGF-I plays a key role in the proliferation of many types of tumour cells, this is less often the case for GH or PRL. The importance of the JAK-STAT signalling pathway, including those molecules activated by GH-R or PRL-R, in leukaemia cells is illustrated by several recent reports. Through this or other signalling pathways, GH or PRL may inhibit or reinforce signals that contribute to progression or arrest of tumour growth. JAK-STAT, however, is not the only pathway used by GH and PRL. GH and PRL, as well as IGF-I, signal through insulin-receptor substrate-1 and also through Shc, Grb2-Sos and the mitogen-activated protein (MAP)-kinase pathway. The complexity of receptor cross-talk is illustrated by experiments documenting inhibition by PRL of epidermal growth factor signalling [83]. It was recently suggested that dysregulation of the newly discovered families of cytokine-inducible signalling inhibitor molecules (CIS) and PIAS (protein inhibitors of activated STAT) may have a role in proliferative disorders. Indeed, these molecules seem to act as negative regulators of cytokine action. They negatively regulate cytokine-induced proliferation but inhibit cytokine-mediated differentiation and growth arrest [84, 85]. Manipulation of hormone levels may have therapeutic value in some haematological diseases. It is therefore important to understand the relative contribution of endocrine and paracrine hormone production. Indeed, most pharmacologic agents that affect hormone secretion in the pituitary are not effective in extrapituitary sites.
4) Many effects of GH, PRL and IGF-I on the haemopoietic system are stimulatory. All three factors can thus be considered for the treatment of bone marrow aplasia, after, for example, radio- or chemotherapy. The place of GH and IGF-I in the management of catabolic states is discussed elsewhere in this issue (see paper by Velkeniers et al.).

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