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Regulation of B and T cell development by anterior pituitary hormones

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Abstract. Hormones produced by the anterior pituitary gland have been implicated in the regulation of primary lymphocyte development. In order to identify endocrine factors involved in that process, several strains of mice with genetic defects resulting in a selective impairment in the production of one or more anterior pituitary-derived hormones have been analysed. This study has resulted in the classification of endocrine hormones into the following four categories: (i) hormones such as prolactin with no apparent effects on primary lymphopoiesis; (ii) anabolic hormones such as growth hormone and insulin-like growth factor-I whose stimulatory effects on primary lymphopoiesis are non-lineage-specific and related to their actions as systemic mediators of growth and/or differentiation; (iii) hormones such as thyroid hormones that have an obligate role in primary B lymphopoiesis; and (iv) hormones such as oestrogens that act as negative regulators of lymphopoiesis.

Key words. Anterior pituitary; lymphopoiesis; thyroid hormones; growth hormone; insulin-like growth factor-I; prolactin; transgenic mice.

Introduction

Lymphocyte development is a dynamic process in which committed lymphoid precursors progress through a series of defined maturational stages before maturing into B and T cells that are distinguished by expression of surface immunoglobulin (Ig) or the T cell receptor (TCR), respectively. Primary, or antigen-independent, B cell development takes place in the intersinusoidal spaces of the medullary cavity in parallel with myelopoiesis and erythropoiesis [1, 2], whereas primary T cell development occurs in the thymus [3–6].

The identification of cell surface determinants that are differentially expressed on developing lymphoid cells has allowed specific stages of B and T cell differentiation to be defined (fig. 1). For example, Hardy and colleagues [7] demonstrated that at least six stages of B cell differentiation can be distinguished based on the differential expression of CD43, CD45R, BP-1, CD24 (heat stable antigen, HSA), and surface IgM and IgD. Within the thymus, the earliest population of triple negative cells, which do not express CD4 or CD8, can be distinguished based on differential expression of the CD44 and CD25 cell surface determinants. Once cells downregulate both of these determinants, they coexpress CD4 and CD8. Subsequently, CD4 helper and CD8 cytotoxic T cells are generated [5].

Lymphopoiesis in the bone marrow and thymus occurs in association with a three-dimensional framework of supporting stromal cells that are the source of a variety of extracellular regulatory signals [1, 2, 4, 6]. For example, stromal cell-derived interleukin (IL)-7 has been shown to play a critical role in the survival and/or growth of lymphoid progenitors [1, 2]. While considerable attention has been placed on the identification and

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characterization of these mediators, there has been a growing appreciation that in addition to extracellular signals produced by the marrow or thymic microenvironments, systemic stimuli derived from extramedullary and extrathymic sources may also affect lymphopoiesis. Particular attention has been focused on the endocrine system in this regard [8–12].

Although interest in the effect of endocrine hormones on lymphocyte development has been rekindled recently, the literature implicating endocrine signals in the regulation of immune cell production and function extends back for at least 30 years. However, many of the early reports on this topic did not distinguish hormonal effects on primary lymphopoiesis from those on secondary differentiation and were performed prior to the development of modern flow cytometric techniques that permit detailed analysis of lymphocyte subpopulations. The aim of this review is to provide an overview of recent work from this and other laboratories which describes the effects of endocrine factors, particularly those derived from the anterior pituitary gland, on primary lymphocyte development.

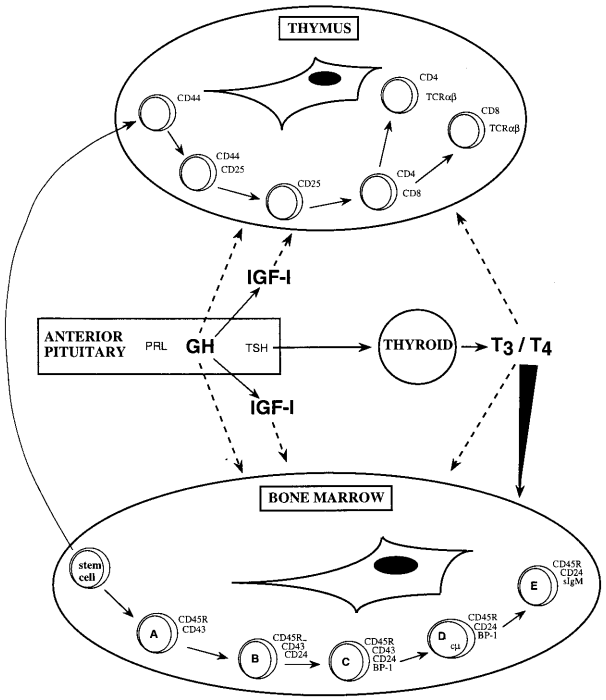

Figure 1. Scheme of primary lymphopoiesis, showing cell surface determinants used to identify B and T lineage cells at different stages of development in the bone marrow and thymus, respectively, and the effects of anterior pituitary derived hormones on those cells. The letters at each stage of B cell development denote the fractions described by Hardy and colleagues [7]. Thyroid hormones have been shown to have an obligate role in B cell development (bold arrow), whereas the stimulatory effects of other hormones, such as GH and IGF-I, on lymphopoiesis are due to their anabolic effects (dotted arrows). The various hormones may act directly on developing lymphoid cells or indirectly through effects on the bone marrow and thymus microenvironments. No effects of hormones such as prolactin (lowercase type) on primary B and T cell development have been demonstrated.

Analysis of lymphopoiesis in hormone-deficient mice

Studies performed in the 1930s revealed that hypophysectomy in the rat resulted in the regression of the thymus [13]. Although the true function of the thymus as the site of primary T cell differentiation was not appreciated at that time, in retrospect, this study provided some of the first evidence that immune cell development could be influenced by products from the anterior pituitary gland. Additional support for this premise has been provided by studies of the Snell dwarf (*dw/dw*) strain of mice. Due to a mutation in the gene encoding Pit-1, a DNA-binding protein required for the expression of genes encoding hormones that include growth hormone (GH), thyroid-stimulating hormone (TSH), and prolactin (PRL), these mice are deficient in production of these hormones [14]. Since insulin-like growth factor-I (IGF-I) and thyroid hormone production is regulated by GH and TSH, respectively, dwarf mice are also IGF-I- and thyroid hormone-deficient. Some of the earliest studies of this strain revealed that their thymus was atrophied and that their marrow was markedly hypocellular [15, 16].

More recent flow cytometric analysis of dwarf mice by Murphy and colleagues suggested that the production of $CD4^+CD8^+$ thymocytes ceases at a relatively early age. Surprisingly, phenotypic analysis of bone marrow B cell populations in dwarf mice was not reported until 1992 and showed that the frequency of the $CD454R^+$/surface IgM^- progenitor pool was severely depressed [17–19]. In retrospect, this result was consistent with a 1971 report that numbers of marrow mononuclear cells were abnormally low in dwarf mice [20].

While these results provided a basis for proposing that lymphopoiesis is dependent upon one or more anterior pituitary-derived hormones, the fact that dwarf mice are deficient in multiple hormones made it difficult to define which one(s) is critical for normal T and B cell development. In order to address this issue, several strains of mice with genetic defects resulting in a selective impairment in the production of anterior pituitary-derived hormones were analysed in our laboratory. Two strains of mice made it possible to assess the effects of GH/IGF-I deficiency on lymphocyte development. As indicated in table 1, little (*lit/lit*) mice have a defect in the gene encoding the receptor for hypothalamic growth hormone-releasing factor, and as a result, so-

Table 1. Characteristics of hormone-deficient mice.

Strain	Defect	Hormone deficiency
Snell dwarf (*dw*/*dw*)	mutation in *pit-1* transcription factor	GH, PRL, IGF-I, TSH, T3, T4
Hypothyroid (*hyt*/*hyt*)	mutation of TSH receptor on thyroid epithelium	T3, T4
Little (*lit*/*lit*)	mutation of GH-releasing factor receptor	GH, IGF-I
IGF-I$^{-/-}$	targeted disruption of *IGF-I* gene	IGF-I
PRL$^{-/-}$	targeted disruption of *PRL* gene	PRL
Hypogonadal	partial deletion of *GnRH* gene	FSH, LH, sex steroids

GH, growth hormone; PRL, prolactin; IGF-I, insulin-like growth-factor-I; TSH, thyroid-stimulating hormone; T3, triiodotyronine; T4, thyroxine; GnRH, gonadotropin-releasing hormone; FSH, follicle-stimulating hormone; LH, lutenizing hormone.

matotrophs in their anterior pituitary gland fail to secrete GH. As expected, the lack of GH results in a severe depression of IGF-I production in these mice. However, their levels of serum TSH and thyroid hormones are normal [21, 23]. Mice in which the gene encoding IGF-I has been disrupted (*IGF-I*$^{-/-}$ mice) permitted an analysis of the specific contribution of IGF-I to lymphopoiesis to be made [24]. The role of thyroid hormones in lymphocyte development was analysed in hypothyroid (*hyt*/*hyt*) mice. This strain has a deficiency in thyroid hormone production due to an inability of thyroid epithelial cells to bind TSH, and their production of thyroid hormones is reduced by up to 90% [25, 26]. Finally, the role of PRL in B and T lymphopoiesis was analysed in PRL knockout (*PRL*$^{-/-}$) mice [27].

The analysis of B and T cell development in these mice has resulted in the classification of the various anterior pituitary hormones, or hormones regulated by them, into the following categories: (i) hormones with no effects on primary lymphopoiesis; (ii) anabolic hormones whose stimulatory effects on primary lymphopoiesis are non-lineage-specific and related to their actions as systemic mediators of growth and/or differentiation; (iii) hormones that have an obligate role in primary lymphopoiesis.

Although the focus of studies in this laboratory has been placed on the identification of hormones that act as positive regulators of lymphocyte development, the immunosuppressive effects of some steroid hormones has long been recognized. Recent studies performed on both pregnant animals and the hypogonadal strain of mice, which are deficient in the production of follicle-stimulating hormone (FSH) and lutenizing hormone (LH), have revealed that sex steroids such as oestrogens are potent negative regulators of primary B lymphopoiesis [28]. In view of these results, hormones that act as negative regulators of lymphopoiesis constitute a fourth category of hormones that affect lymphopoiesis.

Hormones with no effects on primary lymphopoiesis

There is a considerable literature suggesting that hormones such as PRL have a role in potentiating immune responses [8–12], and the expression of the PRL receptor on most bone marrow cells [29, 30] further suggested that it could be involved in the development of hematopoietic cells. However, the analysis of blood cell development in both dwarf and *PRL*$^{-/-}$ mice failed to reveal a role for PRL in either primary lymphocyte development or the production of haematopoietic cells in general.

Initial studies investigated whether or not treatment of dwarf mice with ovine PRL would restore B lymphopoiesis to normal. Following treatment of mice with 100 μg of PRL/day, lymphopoiesis in the bone marrow and thymus was examined. PRL-treated dwarf mice had a significant ($P < 0.025$) increase in total number of marrow cells. However, the frequency of both CD45R$^+$ surface IgM$^-$ and surface IgM$^+$ cells remained depressed [27]. No significant effects of PRL on thymus cellularity or the distribution of CD4 and CD8 expression on dwarf mouse thymocytes was observed (unpublished observations).

Further confirmation that prolactin had little effect on B lymphopoiesis or blood cell development in general was obtained by analysis of the *PRL*$^{-/-}$ mouse. No defects in marrow B cell development, myelopoiesis or thymopoiesis were detected in these animals. In fact, the frequency and absolute number of cells in all of these lineages in *PRL*$^{-/-}$ mice were comparable to values in their heterozygous littermates [27]. This observation is in accord with recent results presented at First Conference on Hormones, Blood Cells and Immunity showing that primary lymphocyte development was normal in PRL-receptor knockout mice. While the possibility that PRL might have effects too subtle to be detected by the assays employed cannot be excluded, these data strongly suggest that PRL does not have an obligate role in primary blood cell development.

Effects of anabolic hormones on primary lymphocyte development

A major aim of many laboratories over the past decade has been to identify stromal cell-derived factors that regulate B cell development, and these efforts have resulted in the identification of multiple stromal cell products that include IL-7 [1, 2]. Studies in our laboratory focused on the characterization of a stromal cell line that secreted a soluble mediator able to support the development of $CD45R^+$ pre-B cells from $CD45R^-$ precursors [31]. Subsequent studies revealed that this activity was due to stromal cell-derived IGF-I [32]. This observation, combined with the fact that IGF-I concentrations in dwarf mice are severely depressed, raised the possibility that defective B cell development in those animals was due to their IGF-I deficiency. Accordingly, dwarf mice were treated with recombinant human IGF-I for 2 weeks, and B lymphopoiesis was assessed. Since IGF-I production is regulated by GH and it mediates many GH effects [33], additional groups of mice were treated with GH as well. The results of these studies demonstrated that, even following 2 weeks of GH or IGF-I treatment, the frequency of B lineage cells in dwarf mice remained depressed [34].

These results suggested that neither GH nor IGF-I are obligate B lymphopoietic factors. In order to investigate this in more detail, B cell development in GH/IGF-I-deficient little mice and *IGF-I*$^{-/-}$ animals was analysed. These studies revealed that the frequency of B lineage cells in these mice was comparable to that in their normal littermates. Although the *lit*/*lit* and *IGF-I*$^{-/-}$ mice are smaller than their normal littermates due to their lack of GH and IGF-I, their absolute number of B lineage cells was normal when values were normalized to the weight of the mice. In addition, no deficiencies in the frequency of marrow myeloid cells or thymocyte subpopulations were observed in the *lit*/*lit* and *IGF-I*$^{-/-}$ mice. Thus, these data strongly suggest that GH and IGF-I are not obligate thymopoietic or myelopoietic factors [35].

These findings appear to contradict results of numerous studies demonstrating that GH and IGF-I can stimulate haematopoiesis and lymphopoiesis both in vitro and in vivo [8–12] and that haematopoietic cells express the GH receptor [36]. For example, treatment of normal mice with IGF-I can increase the total number of bone marrow B lineage cells [37], and both GH and IGF-I have been shown to increase thymus cellularity significantly following their administration to rodents [17, 38–40]. In this regard, Dardenne and colleagues have shown that the thymopoietic effects of GH may be mediated through effects on thymocytes and/or their supporting microenvironment [41]. One way in which these findings can be reconciled is if GH and IGF-I are considered as general anabolic hormones with effects on target cells in multiple tissues that include bone marrow and thymus.

A prediction based on this premise is that the total number of haematopoietic cells in the bone marrow and thymus should increase following GH or IGF-I treatment but that differential effects on a particular blood cell lineage should not be observed. Indeed, in both GH- and IGF-I-treated mice, increases in the absolute number of marrow myeloid and B and thymic T cells occurred. However, the relative frequencies of these lineages remained unaffected by these hormones [34, 37]. A second prediction is that in addition to increases in numbers of haematopoietic cells, an increased in size of other organs should be demonstrable. In fact, the increase in the number of haematopoietic cells occurred in parallel with enlargement in size of many organs as well as overall weight gain of the hormone-treated mice. A final expectation is that in the absence of GH and IGF-I, cell production in all haematopoietic lineages should be normal and proportionate to the size of the animal. This was the case in both *lit*/*lit* and *IGF-I*$^{-/-}$ mice wherein the frequency of CD4- and/or CD8-expressing thymocytes and bone marrow haematopoietic lineages had a normal distribution [34, 35].

This view of how GH and IGF-I act has important implications for the interpretation of studies in which their effects on a particular cell population or tissue are measured. Thus, if in vivo studies are performed, a thorough analysis will reveal the systemic effects of these hormones. However, if only one GH/IGF-I target tissue or organ is studied in isolation, or if a single lineage is analysed in an in vitro system, the general anabolic effects of GH and IGF-I will be overlooked. In this case, the effects on those tissues can be misinterpreted as being specific for a particular organ or cell lineage.

Obligate lymphopoietic hormones

It is logical to propose that the suppressed B cell development in dwarf mice is a result of their hormonal defects, but proof that this is the case depends on showing that one or more anterior pituitary-derived hormones can restore the frequency of B lineage cells to normal. As noted above, GH, IGF-I and PRL failed to do so. However, a consistent finding was that treatment of dwarf mice with thyroxine restored the frequency of B lineage cells to normal and increased marrow cellularity [34]. Analysis of the thyroid hormone-deficient hypothyroid (*hyt*/*hyt*) strain of mice provided further

evidence that thyroid hormones played an important role in B cell development. Like dwarf mice, these animals have a deficiency in $CD45R^+IgM^-$ B cell progenitors, and this defect could be reversed by treatment of mice with thyroxine [35].

The haematopoietic defects in the thyroid hormone-deficient dwarf and *hyt/hyt* mice appeared to be restricted to the B cell lineage, as the frequency and absolute number of myeloid cells and thymocytes in these mice were normal [35]. It should be noted that the observation that the frequency of CD4- and CD8-expressing thymocytes in dwarf mice did not differ from values in their normal littermates is not in agreement with a previous report showing that the frequency of $CD4^+CD8^+$ thymocytes is reduced in the mice [17]. However, in our studies, no thymic defects were ever detected. Conditions under which the mice are raised may account for these differences between laboratories [42, 43]. These results also do not exclude the possibility that, similar to the effects of GH and IGF-I noted above, the anabolic actions of thyroid hormones can result in non-lineage-specific increases in numbers of haematopoietic cells in the bone marrow and thymus [44, unpublished observations].

Additional strains of transgenic mice in which the gene encoding the thyroid hormone receptor has been disrupted have recently been described. The thyroid hormone receptor is a member of a family of hormone-responsive nuclear transcription factors that have a ligand-binding domain and a zinc-finger DNA-binding domain [45, 46]. Distinct forms of the receptor are encoded by two genes, α and β, and alternative messenger RNA (mRNA) splicing can result in multiple receptor isoforms. One critical function of thyroid hormone in cells is to regulate gene expression during development, and this event is influenced by both hormone availability and by the differential expression of particular thyroid hormone receptors at different times during development and at different stages of differentiation [47]. No haematopoietic defects in mice in which the gene encoding the β form of the thyroid hormone receptor was disrupted were reported (48). Two laboratories have independently generated thyroid hormone α knockout mice [49, 50]. Fraichard and colleagues [49] noted in their animals that there was a marked depletion of haematopoietic cells in their bone marrow [49]. It will be of interest to assess whether or not this is due to a depletion of B lineage cells.

There are at least two major issues to be addressed in order to understand how thyroid hormones regulate B cell development. First, the cellular targets of thyroid hormones need to be identified. The thyroid hormone receptors are expressed on cells in most tissues, including B lineage cells (unpublished observations), thereby raising the possibility for thyroid hormone to have direct and indirect effects on B cell development. Preliminary data indicate that at least some hormone effects are directly mediated on the bone marrow, since triiodothyronine enhances B lymphopoiesis in long-term bone marrow cultures that support the differentiation of immature haematopoietic precursors into B lineage cells (unpublished observations). A second major challenge will be to identify genes whose expression is regulated by thyroid hormones. Some of these could be genes whose temporal expression during B lymphopoiesis is already defined or novel genes whose expression is critical for normal B cell development.

Negative regulators of lymphopoiesis

While the above discussion has focused on hormones as positive regulators of lymphocyte development, it has long been recognized that steroid hormones are potent negative regulators of lymphopoiesis. Indeed, administration of corticosteroids to mice results in a profound thymic atrophy. More recently, the role of sex steroids as negative regulators of B lymphopoiesis has been revealed [28].

During the analysis of pregnant mice, it was observed that bone marrow B lymphopoiesis was markedly suppressed and that the export of newly produced B lymphocytes to the periphery was below normal [51–53]. In order to test the hypothesis that sex steroids produced during pregnancy were responsible for these observations, normal mice were treated with oestrogen, progesterone or a combination of the two. The results demonstrated that oestrogen alone is a potent inhibitor of marrow B lymphopoiesis. Progesterone had little effect on lymphopoiesis, but it could enhance the negative effects of oestrogen.

The use of genetically mutant mice deficient in the production of gonadotrophic hormones provided further insight into the role of sex steroids as negative regulators of B cell development [51–53]. Hypogonadal mice have a deletion in the gene encoding gonadotrophin-releasing hormone (table 1), and as a result these mice do not secrete FSH or LH [54]. This in turn results in decreased oestrogen levels in the mice. Consistent with oestrogen being a negative regulator of B lymphopoiesis was the finding that the number of B lineage cells in hypogonadal mice was elevated compared with normal controls. This result suggests that oestrogens may be important regulators of steady-state B cell development [54].

How oestrogen mediates its effects is unknown. However, the negative regulatory effects of oestrogens were only demonstrable in the presence of stromal cells, suggesting that their inhibitory effect is indirectly mediated. Further studies will be needed to define the precise oestrogen effects on the stroma [55].

Concluding remarks

The above results suggest that while many hormones have the potential to stimulate primary lymphocyte development, only thyroid hormones have an obligate role in that process, and their effects are restricted to the B cell lineage.

It is important to note that this conclusion only applies to primary lymphocyte development, which has been the focus of this review. A major question to be addressed is what role hormones have on the regulation of secondary immune development. In fact, there is a considerable, and often confusing, literature indicating that hormones can affect lymphocyte survival, proliferation and/or secretion of cytokines or immunoglobulins [8–12]. The availability of the various hormone-deficient mice and recombinant or pure hormone preparations should renew interest in evaluating the effect of hormones on functional lymphocyte responses. If particular hormones are shown to have a role in lymphocyte functional responses, it will be particularly interesting to assess whether or not a decline in their production, as could occur during ageing, contributes to the decline of the immune system in older individuals.

Finally, while the above studies have been performed in rodents, it will be important to ultimately ascertain whether or not the results obtained are applicable to humans as well.

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