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Introduction: hormones, blood cells and immunity, with special reference to prolactin, growth hormone and insulin-like growth factor-I

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To everybody's surprise, the growth hormone receptor (GH-R) turned out to be the first member of the cytokine-haemopoietin-receptor family. There is a strong homology between GH-R and the prolactin (PRL)-R. Nobody would accept homology between receptors for hormones and bona fide interleukins as convincing evidence for including GH or PRL in the group of lymphohaemopoietic growth and differentiation factors. The main basis for the recent interest in the role of GH and PRL in the immune system was a series of papers by E. Nagy and I. Berczi that described broad immunodeficiency in hypophysectomized rats and restoration by GH or PRL. These and many studies of the 1980s have been critically reviewed by R. Gala [1]. More recently, receptors for GH and PRL were identified on several leukocyte subsets. Thus, a direct effect of GH and PRL on these cells was possible. Also, receptors for the insulin-like growth factors (IGF) are widely expressed on leukocytes (IGF-I has to be included in a study on GH as it mediates most effects of GH). Many data published before 1996 are summarized in ref. 2. Expression of GH and PRL, as well as IGF-I, by several types of leukocytes was also demonstrated (reviewed in refs 2 and 3). Moreover, expression of the factors and their receptors could often be correlated with differentiation and activation [2]. Data, mainly from rodents, favoured the proposal that GH, PRL and IGF-I were indeed cytokines, as they were produced by leukocytes and acted on blood cells as growth or differentiation factors. Data in humans were scarce: there was no reported physiopathological link between GH or PRL and the lymphohaemopoietic system.

In 1997, the European Science Foundation sponsored the organization of a conference on hormones, blood cells and immunity with special concern for PRL, GH and IGF-I (Obernai, 3–8 October). Highlights from this conference are presented in this issue of *CMLS*. Together with recent reviews and original articles published elsewhere and quoted here, this multi-author review covers the state of the art in the field of GH, PRL and their receptors, as well as IGF-I, with special concern for the lymphohaemopoietic system in rodents and in humans.

GH and PRL are expressed mainly in the pituitary gland. The paper by M. de la Hoya et al. (p. 1059) reviews transcription factors involved in the differentiation of GH and PRL cells in the pituitary. Interestingly, some of these factors are hardly expressed in other tissues. Their expression there is not related to hormone expression. Conversely, extrapituitary hormone expression is not dependent on the same transcription factors as in the pituitary.

GH-R and PRL-R share homology with other receptors of the cytokine-haemopoietin-receptor family. They also signal mainly through the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) cascade. There are fewer JAK kinases than members in the receptor family (at least 20). Similarly, there are only 7 STAT factors in mammals. It is thus no surprise that GH-R and PRL-R actually share JAKs and STATs with other receptors. This provides a first basis for redundancy in the cytokine network, to be discussed in more

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detail below. L.-y. Yu-Lee et al. review their recent findings in this field on p. 1067. Other reviews on JAKs and STATs (not concerned primarily with GH-R or PRL-R) were published recently by Pellegrini and Dusanter-Fourt [4] and by Darnell [5].

The obvious strategy to examine the possible role of a given factor is to generate transgenic animals overexpressing the factor or not expressing the factor or its receptor(s). On p. 1076, Foster et al. present their own data on the development of the immune system in PRL knockout mice. They also review data in other systems, including Pit-1-deficient dwarf mice which have haematological and immune deficits. These mice lack pituitary GH, PRL and TSH. Taken together, the data clearly indicate that thyroid hormones have an obligate role in B-lymphopoiesis, that GH and IGF-I have stimulatory effects that are not lineage-specific and that PRL has no measurable effect on primary lymphopoiesis. The latter conclusion is further strongly supported by the detailed studies in PRL-R knockout mice by B. Bouchard et al. (unpublished). These mice do not show any haematological or immune deficits.

S. van Buul-Offers and R. Kooijman (p. 1083) extensively review the effects of GH and IGF on the immune system, with particular attention to the IGF-binding proteins. In the past, syndromes of GH or PRL overproduction or deficit were not related to any haematological or immune dysfunction. Velkeniers et al. (p. 1102) agree with this view. However, they note that many syndromes have not been properly investigated in this respect. There have also been recent hints from animal research and from clinical studies that PRL plays an aggravating role in some autoimmune diseases. For instance, flares in lupus erythematosus correlated in some cases with high levels of PRL.

As is the case with normal leukocytes, many lymphoma or leukaemia cells from rodents or humans express receptors for GH-R, PRL-R or IGF-R. Accordingly, Hooghe et al. (p. 1095) suggest that GH-R, PRL-R or IGF-R may in the future be recognized as diagnostic markers for some forms of lymphohaemopoietic malignancies. Some leukaemic cells also express GH, PRL or IGF-I. These observations add another level of complexity to the physiopathology of these diseases: these factors may act on malignant cells, for example as paracrine or autocrine growth factors. They may also modulate antitumour immune responses.

Taken together, the papers in this issue provide evidence that GH, PRL and IGF-I can have effects on normal and transformed leukocytes after binding to specific, functional receptors. At the same time, it must be emphasized that there is no compelling evidence in rodents or humans that endocrine GH, PRL or IGF-I specifically act on certain lineages during the development of the lymphohaemopoietic system. Paracrine-autocrine effects are also ruled out in PRL-R knockout mice. These factors may still act at later stages and modulate immune responses. Specific effects, for instance on Th1 and Th2 responses, have been observed (Hooghe et al., unpublished). The lack of symptoms in $PRL^{-/-}$ and in $PRL\text{-}R^{-/-}$ mice is somewhat surprising in view of several in vitro and in vivo studies. Lessons from $IL\text{-}2^{-/-}$ and $TNF\text{-}R^{-/-}$ mice suggest that a role for PRL, for instance, may be obvious only in double knockout mice where more than one factor or receptor is missing. Indeed, redundancy is a key feature of the cytokine network so that a given factor is dispensable in many situations. Additional receptors may still be discovered. For instance, there is preliminary evidence for a specific receptor for 16-kDa PRL [6]. The study of hormone variants and receptor isoforms is still in its early stages. The contribution of PRL to autoimmune diseases has still to be delineated. Several sex-related effects in females have been ascribed to oestrogens. As oestrogens stimulate PRL secretion, it remains possible that some effects of oestrogens are mediated through prolactin.

Finally, as many effects of GH, PRL or IGF-I reported so far are stimulatory, the possibility is being explored that these factors may be of interest in the treatment of bone-marrow failure or some forms of immunodeficiency. In addition to their anabolic properties, GH and IGF-I may have specific physiological or pharmacological effects, in particular in the field of immunohaematology. As pointed out by B. Velkeniers et al. (p. 1102), they certainly do not offer miracle solutions for AIDS or ageing, for example, but they should be considered, together with PRL, as full members of the cytokine network and, as such, candidates (or targets) for immunotherapeutic intervention.

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