Thymic Endocrinology-Part 2

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Abstract

The concept of thymic endocrinology describes a bidirectional effect: the thymic hormones which circulate and significantly affect the immunomodulatory function of the body, and the action of the other hormones derived from the pituitary, adrenal, gonads and thyroid gland on the thymocytes, thymic epithelial cells and the thymic stromal cells. Apart from this there is also an extensive paracrine and autocrine endocrine signal network within the intrathymic environment involving interleukins and thymic peptides .This review attempts to delve into the under-standing of this intrinsic relationship between the thymus gland and the endocrine system at large.

Paracrine and Autocrine Circuits of the Thymus

[1]Functional circuits in both the lymphoid and microenvironmental compartments of the thymus in-volving intrathymic production of hormones and peptides which subsequently control various path-ways of thymocyte development and secretion have been identified.

Cytokines

The major intrathymic influences which affect thymocyte growth and development have been identified to be the interleukin signals from IL1 alpha and beta, IL2, IL6, GM-CSF,IFN-γ and perhaps IL3 secreted by the thymic epithelial cells. These intrathymic secretions generate an intrathymic language which regulate various aspects of thymocyte proliferation and maturation.

Interleukins (IL~ a and/3) stimulate the proliferation of thymic epithelial cells. IL1 induces preferential zinc uptake into the thymic epithelial cells. Zinc is associated with metallothionein gene induction and has a role in the thymocyte proliferation. IL1 induces metallothionein mRNA. IL1 induces thymic epithelial cells to secrete thymulin. IL1-Thymulina complex potentiates the proliferative responses of T-cells.[1] Gamma interferon and a TNF have been found to have minimal effect by themselves but do potentiate the effect of IL1.[2] GM-CSF also has a synergistic action in the augmentation of IL action in the thymocytes.[3] IFN-γ can induce MHC class II expression by cultured TEC as also expression of ECM ligands and receptors which consequently modulate TEC-thymocyte adhesion.[4]

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Thymic Hormones

The three thymic hormones thymosin-α1, thymopoietin, and thymulin affect thymocyte proliferation and maturation in a paracrine manner.

Interestingly evidence from hybridisation and immunocytochemistry have demonstrated the presence of intrathymic production of prolactin and growth hormone.[5] Production of Pit 1/GHF1 transcription factor (which control the expression of GH and prolactin) have also been demonstrated.[6]

Exogenous or thymus-derived GH initiates or enhances a circuit in the thymus involving intrathymic production of IGF-I and its receptor.[7] which subsequently controls thymulin secretion, TEC/thymocyte adhesion by GH and increase in IL-6 production by thymocytes.

LH and FSH and LH-RH peptides have been extracted from human thymocytes.[8]

It has been advocated that some amount of glucocorticoid production occurs in the thymus by the thymic epithelial cells and thymocytes which express GC-synthetic enzymes and are regulated independently of the adrenals. Whether this amount is sufficient to affect thymocyte development in the presence of adrenal glucocorticoids, however, is unknown. The demonstration of intrathymic production of CRH along with ACTH and corticosterone by TEC raises the hypothesis that a complete circuit analogous to that of the hypothalamus-pituitary-adrenal axis, may be present within the thy-mus.[9]

Documentation of local production of TRH as also the intrathymic expression of the TRH receptors makes it plausible that an autocrine/paracrine TRH-mediated circuit exists in the thymus.[10] Intrathymic expression of the neuropeptide VIP which enhances the antigen-induced differentiation of CD4+CD8+ immature thymocytes to CD4+ mature thymocytes has been demonstrated.[11] Other hormones which have been found to have originating source within the thymus are Somatostatin, Vasopressin ,Oxytocin, Met/Enkephalin, Endorphin and VIP.

Thymo-Pause

A unique feature of the thymus is that its age related atrophy begins with the onset of puberty. The highest rate of age-dependent thymic involution is observed immediately after puberty, when sex hormone production reaches its peak. The rate of atrophy is greater in males than in females, suggesting that androgens may have a more dramatic impact. The aged thymus displays marked alterations in the cellularity of the stroma characterized by reduction of proliferative and self-renewing capacity of TEC and increase in adipocytes and fibroblasts causing progressive fibrosis and fatten-ing of thymic tissue. The old TEC that persist now downregulate the expression of genes that play important roles in the maintenance, function and/or homeostasis of TEC.[12] Oxygen-free radicals and/or aerobic metabolism also have a role to play in age-dependent thymic atrophy. Thymic stromal cells have been found to be deficient in the H_2O_2 -reducing enzyme catalase which could be one of the causes of accelerated atrophy compared to other glands.[13] The process of atrophy is a progressive one and by 50 years of age approximately 80% of the thymic stromal space is dysfunctional and composed of adipose tissue.[14] This age related atrophy of the thymus has been advocated as one of the major reasons of geriatric immunodeficiency.

In the COVID-19 pandemic of Corona virus a typical pattern has been observed from around the world wherein on one end of the spectrum the rates of mortality and morbidity in the elderly have been much more than in the younger population and in the other end of the spectrum in the paediatric population, though young children, particularly infants are vulnerable to infection, the clinical manifestations of children's COVID-19 cases were generally much less severe in comparison to adult patients.[15] The role of the activity of the thymus in this context is an area that needs further analysis. In addition to age-dependent atrophy other factors like stress, infection, glucocorticoid treatment, chemotherapy and irradiation can also cause transient degeneration of TECs mainly by the action on developing T cells. Depletion of developing thymocytes, loss of cross talk, induction of apoptosis and thymic involution are some of the mechanisms involved.[16]

Clinical Potential

The thymus has been studied as a key organ which modulates the bidirectional relationship between the immune and the endocrine systems. It is possible that thymic hormones, especially THF, can be harnessed for the management of viral infections. The use of THF as an anti-viral therapy has been studied in various murine models. In recent years, T cells have been studied as means of treating viral diseases such as chikungunya fever.[17] THF may have a potential adjuvant role in managing COVID-19.

Thymosin α1 has showed antiviral, angiogenic and wound-healing activities.[18] Thymosin beta-4 has been used as a doping agent in sports.[19] It regulates the inflammatory response at various levels, and influences various signalling pathways including the NIK/NF-kappa B pathway.[20] Its recommended name is timbetasin. Timbetasin has also been shown to induce hair growth in mice and may be used as an aduvant to boost immune response in infection. It can also be of therapeutic value in the setting of acute myocardial damage due to its action on wound healing and angiogenesis.

The bioactive tetrapeptide goralatide which corresponds to the N-terminus of thymosin β4, is also a physiological regulator of haematopoiesis and inhibits the entry into the S-phase of murine and human haematopoietic stem cells and may reduce the damage to specific compartments in the bone marrow resulting from treatment with chemotherapeutic agents, ionizing radiations, hyperthermy or phototherapy. Thymulin has shown promising results in experimental models of lung diseases and as an analgesic peptide.

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