Mechanism of Hormone Production in Pituitary Cells and Pituitary Neoplasms; Synergistic Actions of Transcription Factors

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Recent technological development has disclosed various transcription factors in the pituitary glands. The cloning of Pit-1, homeodomain containing nuclear binding transcription factors stimulated the subsequent discoveries of many factors participating in the transcription for the specific pituitary hormones. These include Pituitary homeobox1 (Ptx1), Prophet of Pit-1 (Prop-1), NeuroD1, steroidogenic factor-1 (SF-1) and DAX-1. These factors have been shown not only to interact but also to function with various receptors synergistically to promote specific hormones, such as GH-PRL-TSH group, POMC and gonadotropin (FSH/LH).

Key words: Transcription factors, Pituitary gland, Hormone production, Molecular biology, Hormone receptor

I. Introduction

The mechanisms of the specific hormone production of the endocrine cells have been the target of research since the techniques to identify the specific hormones were introduced, i.e. immunohistochemistry and in situ hybridization [14]. Since immunohistochemistry was first applied to the pituitary gland as a target tissue, the question of how the particular cells produced particular hormones has been frequently focused on the pituitary gland [14]. Recently, the molecular mechanisms of protein production have been clarified very rapidly, especially since investigation of transcription factors on the pituitary differentiation stimulated this research field, specifically after the introduction and cloning of Pit-1 (GHF/1) by Adler et al. [1] and Theill et al. [29]. The study of Pit-1 has stimulated the investigation of the other transcription factors as listed in Table 1.

This review article describes the mechanisms of functional differentiation of the pituitary glands, cells and the neoplasm.

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II. Transcription Factor Group 1
—Homeodomain Containing Family—

Pit-1

This group of transcription factors was first cloned and designated as Pit-1 (GHF-1). This is a nuclear binding protein containing homeodomain, homeobox and POU domain with 3 isoforms, Pit-1α, Pit-1β and Pit-1T [7, 10, 15]. Pit-1 has been reported with particular specificity for GH, PRL and TSH production in the pituitary glands and pituitary neoplasms [23]. Pit-1T has been pointed out to have a functional relationship with TSH production [22]. In human pituitary adenomas, Pit-1 was frequently localized in the nuclei in GH, PRL and TSH secreting adenomas. It is of particular interest that GH secreting adenomas and TSH secreting adenomas are frequently multihormonal with the combination of GH, PRL and TSH. It is also noteworthy that PRL secreting adenoma is monohormonal. The fact that some nonfunctioning adenomas with frequent glycoprotein subunits are positive for Pit-1 remains to be further investigated [16], but the possibility of dedifferentiated GH cell lineage has been postulated because human GH cells frequently contain glycoprotein αSU and FSH/LhβSU [17, 24]. For Pit-1, several synergistic factors have been clarified. Such
Table 1. Lists of transcriptional factors

<table>
<thead>
<tr>
<th>Transcription factors</th>
<th>Promoted transcripts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pit-1</td>
<td>GH PRL TSH</td>
</tr>
<tr>
<td>Prophet of Pit-1 (Prop-1)</td>
<td>Pit-1, TSH, Gn, POMC (Pit-1 independent)</td>
</tr>
<tr>
<td>Pituitary homeobox 1 (ptx1)</td>
<td>GH PRL POMC TSH Gn</td>
</tr>
<tr>
<td>SF-1 (Ad4BP)</td>
<td>Gn (adrenal steroidogenesis)</td>
</tr>
<tr>
<td>DAX-1</td>
<td>Gn (adrenal steroidogenesis)</td>
</tr>
<tr>
<td>NeuroD-1</td>
<td>POMC</td>
</tr>
<tr>
<td>Leukemia inhibitory factor (LIF)</td>
<td>POMC</td>
</tr>
</tbody>
</table>

Fig. 1. Schematia drawing of functional differentiation of anterior pituitary cells and synergistic action of Ptx1 with other factors.

Table 2. Lists of synergistic co-factors for transcription factors

<table>
<thead>
<tr>
<th>Nuclear receptor superfamily</th>
<th>Promoted transcripts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extrogen receptor (ER)</td>
<td>PRL</td>
</tr>
<tr>
<td>Thyroxine receptor (TR)</td>
<td>GH</td>
</tr>
<tr>
<td>Retinoic acid receptor (RAR)</td>
<td>GH</td>
</tr>
<tr>
<td>Retinoid X receptor (RXR)</td>
<td>TSH</td>
</tr>
<tr>
<td>Cell membrane receptor</td>
<td></td>
</tr>
<tr>
<td>Growth hormone releasing</td>
<td></td>
</tr>
<tr>
<td>hormone receptor (GnRH-R)</td>
<td>GH</td>
</tr>
<tr>
<td>Dopamine 2 receptor (D2R)</td>
<td>PRL</td>
</tr>
</tbody>
</table>

Pituitary homeobox 1 (Ptx1)
Along the line of homeodomain, homeobox, POU domain containing transcription factors, Ptx1 has been recently reported as a factor to promote the production of POMC [12]. Later, the same research group reported that in addition to POMC, Ptx1 protein is localized in other hormone secreting cells in the murine pituitary glands and in known pituitary cell lines [30]. We have also confirmed with our own specific anti-Ptx1 antibody that Ptx1 is localized in the intermediate lobe and various hormone secreting cells in the anterior lobe [11]. Ptx1 is also expressed in various types of human pituitary adenomas including GH, PRL, TSH and POMC secreting adenomas. It is also present in nonfunctioning adenomas [28]. These findings suggest that Ptx1 is rather a universal transcription factor which appears in very early fetal development and functions with synergistic actions by other co-factors.

Prophet of Pit-1 (Prop-1)
Prop-1 has been identified as an early enhancer factor for Pit-1 and an early transcription factor for Pit-1 independent TSH, POMC and gonadotropin [27]. Recently, a few families of dwarfism have been reported to be due...
III. Transcription Factors Group 2

—Without Homeodomain—

NeuroD1, SF-1 and DAX-1

These factors are also nuclear binding proteins without homeodomain sequences. NeuroD1 is a basic helix-loop-helix (bHLH) factor expressed in the endocrine cells of the pancreas and in a subset of neurons. NeuroD1 has been reported as a cofactor which functions synergistically with Ptx1 toward the production of POMC [21]. SF-1 and DAX-1 are the nuclear binding proteins for the production of adrenocortical steroids. SF-1 has also been designated as Ad4BP [4, 8]. Interestingly, these steroidogenic factors are localized in pituitary gonadotrophs [2]. In SF-1 knockout mouse, the pituitary glands lacked gonadotropin [9]. In human pituitary adenomas, gonadotropin secreting adenomas and the nonfunctioning adenomas with gonadotropin subunits show higher expression of SF-1 and suggest its involvement in gonadotropin production by the synergistic action with Ptx1. The expression of DAX-1 in the pituitary cells and the pituitary adenomas is under current investigation. Leukemia inhibitory factor (LIF) is a cytokine which regulates the development of the pituitary gland. Its deprivation enhances the development of POMC [31].

IV. Synergistic Actions of the Transcription Factors

The development of the pituitary cells consists of three lineages, i.e. GH-PRL-TSH, POMC, and FSH/LH. The scheme shows the current status of synergy for the transcription factors. Ptx1 is most likely basic factors and synergizes with Pit-1 for GH-PRL-TSH lineage, with NeutoD1 for POMC lineage, and with SF-1 and DAX-1 for FSH/LH.

V. References


