Annals of Anatomy 195 (2013) 374–384

Contents lists available at Science Direct

Annals of Anatomy

Journal homepage: www.elsevier.de/aanat

Research article

# The expression of AIB1 correlates with cellular proliferation in human prolactinomas

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ARTICLE INFO

Article history:
Received 11 October 2012
Received in revised form: 11 January 2013
Accepted 12 January 2013
Available online 28 February 2013

Keywords:
Adenoma
Pituitary
Prolactinomas
Estrogen
Estrogen receptors
AIB1

SUMMARY

Estrogens as well as various growth factors strongly influence the development and growth of prolactinomas. However, the molecular mechanisms by which extracellular factors trigger proliferation are not well known. Amplified in breast cancer 1 (AIB1), also known as steroid receptor coactivator 3 (SRC-3), belongs to the p160/SRC family of nuclear receptor coactivators and is a major coactivator of the estrogen receptor. Here we report that the estrogen receptor coactivator AIB1 is overexpressed in human prolactinomas and correlates with the proliferation antigen and estrogen receptor α (ERα). Of the 33 pituitary tumors evaluated in women, 30% corresponding to hyperproliferative tumors, contained an enriched population of prolactin-positive cells and hence were further classified as prolactinomas. All prolactinomas showed positive for both ERα and AIB1. Moreover, AIB1 and cellular proliferation were indicative of the cell cycle status of tumors: the nuclear expression of AIB1 was correlated with positive cellular nuclear antigen (PCNA) expression, the cytoplasmic localization of AIB1 correlated with active caspase-3. These new results demonstrate for the first time that AIB1 is expressed in prolactinomas and suggest its participation in the regulation of proliferation and apoptosis of tumoral cells. Because aromatase expression is also enhanced in these prolactinomas and it is involved in the local production of estrogens, both mechanisms, ERα/AIB1 and aromatase, could be related.

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## 1. Introduction

Several coactivator proteins have been identified and implicated in the mechanisms of the transcriptional activation of estrogen receptors and are therefore now considered important modulators of hormonal action (Lee and Chen, 2000; Mitsiades et al., 2002; Nagy et al., 2003; Chang et al., 2006). Consequently, different levels of expression of hormone-dependent tumors to sex steroids could be strongly influenced by the relative amounts of coactivator proteins such as AIB1 (Mukopadhyay et al., 2003). Amplified in breast cancer 1 (AIB1), also known as steroid receptor coactivator 3 (SRC-3), is a member of the p160 coactivator family and plays an important role in cell growth, reproduction, metabolism, and cytokine signaling (Wang et al., 2000; Xu et al., 2000; Zhou et al., 2003). It is a major co-activator of the estrogen receptor (ER) in human breast cancer cell lines (Takeshita et al., 2001), is also overexpressed in several types of cancers, including breast and ovarian (Anzick et al., 1997; Kuchipudi et al., 2008), pancreas (Anzenbacher et al., 2001), gastric (Sakakura et al., 2000), pancreas (Chakrabarti et al., 2000; Ueda et al., 2004), liver (Wang et al., 2002) and colon cancers (Xie et al., 2007). When overexpressed in mammary epithelial cells, AIB1 can function as an oncogene in mouse models (Torres-Arzayus et al., 2004), promoting advanced tumors of various subtypes.

Prolactinomas are hormone-dependent tumors that originate in the lactotrophs of the pituitary gland and constitute the most common endocrine tumors. Chronic treatment with estradiol is known to induce pituitary hyperplasia and prolactinomas (Gomez et al., 1988; Nonogaki et al., 2002; Meinsma, 2003; Medina and Spencer, 2005; Mengesha et al., 2006). Moreover, estradiol stimulates the proliferation of prolactin-producing cells (Lloyd et al., 1979; Pasco et al., 1980) and, interestingly, ER expression in human prolactinomas correlates with proliferation markers and tumor growth (Schwarzenbach

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http://dx.doi.org/10.1016/j.aanat.2013.01.009