



Research article

The expression of AIB1 correlates with cellular proliferation in human prolactinomas

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SUMMARY

Estrogens as well as certain growth factors strongly influence the development and growth of prolactinomas. However, the molecular mechanisms by which extracellular factors trigger prolactinomas are not well known. Amplified in breast cancer 1 (AIB1), also known as steroid receptor co-activator 3 (SRC-3), belongs to the p160/SRC family of nuclear receptor co-activators and is a major co-activator of the estrogen receptor. Here, we report that the estrogen receptor coactivator AIB1 is overexpressed in human prolactinomas and correlates with the detection of aromatase and estrogen receptor α (ER α). Of the 87 pituitary tumors evaluated in women, 56%, corresponding to hyperprolactinemic women, contained an enriched population of prolactin-positive cells and hence were further classified as prolactinomas. All prolactinomas stained positive for both ER α and AIB1. Moreover, AIB1 sub-cellular distribution was indicative of the cell-cycle status of tumors; the nuclear expression of AIB1 was correlated with proliferative markers whereas the cytoplasmic localization of AIB1 coincided with active caspase-3. Thus, our 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 estradiol, both mechanisms, ER-AIB1 and aromatase could be related.

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1. Introduction

Several co-activator 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 (Leo and Chen, 2000; Misiti et al., 1998; Nagy et al., 1999; Shang et al., 2000). Consequently, differential responses of hormone-dependent tumors to sex steroids could be strongly influenced by the relative amounts of co-activator proteins such as AIB1 (Hudelist et al., 2003). Amplified in breast cancer 1 (AIB1), also known as steroid receptor co-activator 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 (Tikkanen et al., 2000), is also overexpressed in several types of cancers, including breast and ovarian (Anzick et al., 1997; Kurebayashi et al., 2000), prostate (Gnanapragasam et al., 2001), gastric (Sakakura et al., 2000), pancreas (Ghadimi et al., 1999; Henke et al., 2004), liver (Wang et al., 2002) and colon cancers (Xie et al., 2005). When overexpressed in mammary epithelial cells, AIB1 can function as an oncogene in mouse models (Torres-Arzuay et al., 2004), producing adenocarcinomas 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 (Gooren et al., 1988; Heaney et al., 2002; Molitch, 2001; Phelps and Hymer, 1983; Wingrave et al., 1980). Moreover, estradiol stimulates the proliferation of prolactin-producing cells (Lloyd et al., 1975; Perez et al., 1986) and, interestingly, ER expression in human prolactinomas correlates with prolactin synthesis and tumor growth (Stefaneanu

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