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Review

Intracrinology of estrogens and androgens in breast carcinoma

Hironobu Sasano*, Takashi Suzuki, Yasuhiro Miki, Takuya Moriya

Department of Pathology, Tohoku University School of Medicine, 2-1 Seiryou-machi, Aoba-ku, Sendai 980-8575, Japan

Abstract

Intratumoral metabolism and synthesis of biologically active steroids such as estradiol and 5α-dihydrotestosterone as a result of interactions of various enzymes are considered to play very important roles in the pathogenesis and development of hormone-dependent breast carcinoma. Among these enzymes involved in estrogen metabolism, intratumoral aromatase play an important role in converting androgens to estrogens *in situ* from serum and serving as the source of estrogens, especially in postmenopausal patients with breast carcinoma. However, other enzymes such as 17β-hydroxysteroid dehydrogenase (17β-HSD) isozymes, estrogen sulfatase (STS), and estrogen sulfotransferase, which contribute to *in situ* availability of biologically active estrogens, also play pivotal roles in this intratumoral estrogen production above. Androgen action on human breast carcinoma has not been well-studied but are considered important not only in hormonal regulation but also other biological features of carcinoma cells. Intracrine mechanisms also play important roles in androgen actions on human breast carcinoma cells. Among the enzymes involved in biologically active androgen metabolism and/or synthesis, both 17β-hydroxysteroid dehydrogenase type 5 (17βHSD5; conversion from circulating androstenedione to testosterone) and 5α-reductase (5αRed; reduction of testosterone to DHT (5α-dihydrotestosterone) were expressed in breast carcinoma tissues, and *in situ* production of DHT has been proposed in human breast cancer tissues. However, intracrine mechanisms of androgens as well as their biological or clinical significance in the patients with breast cancer have not been fully elucidated in contrast to those in estrogens.

Keywords: Estrogen; Androgen; Breast; Cancer; Intracrinology

Contents

1. Introduction

1.1. Development of intracrinology

Biologically active hormones, whether peptides or steroids, are synthesized and secreted from the endocrine organs such as adrenal cortex, or ovary, or pituitary glands. These hormones are transported through the circulation, and act on their target tissues where their specific receptors are expressed (Fig. 1). This system of hormone actions has been called "endocrine", and various biological/clinical features of endocrine target tissues are well-known to be influenced by plasma concentration of the biologically active hormones. Therefore, in the fields of endocrinology, it is very important to evaluate serum or urinary concentrations of hormones in order to obtain a better understanding of physiology and pathology of hormones actions. These locally produced hormones can also act in the same cell (autocrine) or neighboring cells (paracrine) without their release into the circulation.

However, it is also true that a large proportion of androgens in men (approximately 50%) and estrogens in women

* Corresponding author. Fax: +81 22 273 5976.
E-mail address: hsasano@patholo2.med.tohoku.ac.jp (H. Sasano).

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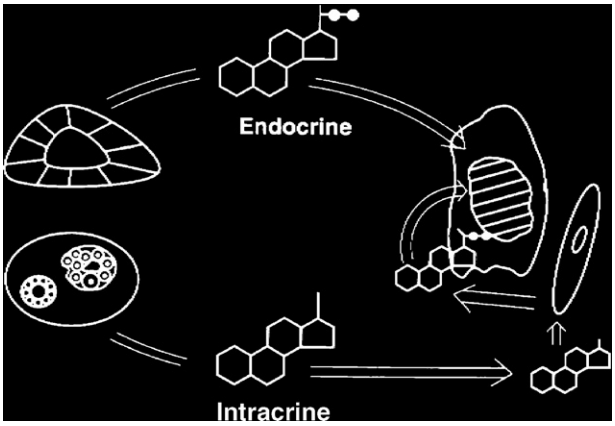

Fig. 1. Illustrations of intracrine and endocrine mechanisms. In endocrine mechanism, biologically active hormones are produced in the endocrine organs, transported through the circulation to the target tissues where they exert their effects. In contrast, in an intracrine mechanism, biologically active hormones are locally converted from biologically inactive precursor hormones produced in the endocrine organs in the tissues where they exert their effects.

(approximately 75% before menopause, and close to 100% after menopause) were produced in peripheral hormone-target tissues from abundantly present circulating precursor steroids [1], where the enzymes involved in the formation of androgens and estrogens are expressed (Fig. 1). These locally produced bioactive androgens and/or estrogens exert their action in the cells where synthesis occurs without release in the extracellular space including circulation. This phenomenon is different from the classical concept of endocrinology such as autocrine, paracrine, and endocrine. This mechanism has been termed "intracrine". It is Labrie and colleagues who elegantly described the formation of active androgens such as dehydrotestosterone (DHT) from the inactive adrenal precursors, dehydroepiandrosterone (DHEA), (DHEA-S (sulfate)) and/or androstenedione locally in the some tissues or cells in adenocarcinoma of the prostate where biosynthesis takes place without release into the extracellular space as "intracrine activity" [1,2].

It then becomes very important to evaluate physiological and/or pathological significance of this intracrine activity compared to endocrine activity. In classical endocrine systems, among those produced and secreted from the endocrine organs, only a small amount of hormones secreted is in general utilized in the target tissues or exerts their effects. The great majority of these hormones is actually metabolized or converted to inactive forms. In contrast, an intracrine system requires minimal amounts of biologically active hormones to exert their maximum hormonal effects. Therefore, the intracrine system is considered a markedly efficient mode of hormone action and plays an important role, especially in the development of hormone-dependent neoplasms including human prostate, breast, endometrial, and ovarian malignancies. It is also important to note that, in an intracrine system, serum concentrations of hormones do not necessarily reflect the local hormonal activities in the target tissues. Therefore, it becomes very important to study how the hormones are metabolized and/or synthesized in the tissue where they exert their actions.

In this review, we summarize intratumoral production of sex steroids including estrogens and androgens in human breast carcinoma tissues, and discuss the potential biological and/or clinical significance of intratumoral production of sex steroids in these carcinomas.

1.2. Intracrinology of estrogens in breast cancer

The great majority of human breast carcinomas express estrogen receptor (ER) in carcinoma or parenchymal cells. These cases are termed hormone- or estrogen-dependent breast carcinoma, and estrogens, especially 17β-estradiol (E2), a biologically potent estrogen, contribute greatly to the growth and development of carcinoma cells and some of these carcinoma cases actually require estrogens for their continued growth and other biological behaviors [3].

It then becomes very important to determine the possible sources of these estrogens that influence various biological behaviors of breast cancers. It is well-known that estradiol originated from different sources before and after the menopause in women. In premenopausal women, the ovary or membrana granulosa of dominant follicles is the main source of abundant circulating estrogens [4,5]. However, as mentioned above after menopause, estrogens are produced primarily through conversion of androgens of both adrenal and ovarian origins, especially of zona reticularis origin of adrenal cortex [6]. The conversion of androgens to estrone occurs principally in peripheral tissues, including skin [7], muscle [8], fat [8], and bone [9]. This conversion is catalyzed by the aromatase enzyme complex [3,5]. However, the great majority of estrone in circulation, including postmenopausal women, is present as sulfated form or estrone sulfate (E1-S) and steroid sulfatase (STS) hydrolyzes circulating E1-S to E1 in various human tissues [10,11]. Estrogen sulfotransferase (EST) (*SULT 1E1* or *STE* gene) is a member of the superfamilly of steroid-sulfotransferases, and sulfonates estrogens to biologically inactive estrogen sulfates [12–14]. Therefore, EST and STS play very important roles in maintaining an availability of biologically active estrogens in the tissues. Estrone is subsequently reduced to 17β-estradiol by 17β-hydroxysteroid dehydrogenase (HSD) type 1, which is also widely distributed in various peripheral tissues [15–17].

Increased peripheral conversion of androgens to estrogens may result in elevated serum levels of estrogens. Therefore, numerous studies have been performed to examine the subtle differences of serum estrogen concentrations between breast cancer patients and their age matched control population. Several epidemiological studies did indicate that plasma estradiol, adrenal androgens, and testosterone levels are higher in women who will develop neoplasms over a period of several years than in those who do not [18]. However, results of other studies [19,20] were not necessarily consistent with those above.