Intracrinology and gastric cancer

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Introduction

Gastric cancer (GC) is one of the most common cause of cancer deaths worldwide diagnosed more often in men than women. The increased incidence of this tumor in men cannot be explained by any of known gender differences or environmental factors, therefore the growth of GC may be regulated by sex steroid hormones [1]. In fact, several studies demonstrated the protective role of estrogens, especially 17β-estradiol (E2) in the etiology of GC and furthermore, the presence of both, estrogen and androgen receptors has been detected in normal and cancerous gastric mucosa [1]. Findings focused on sex steroid biology revealed that large amounts of estrogens and androgens are produced locally in various peripheral tissues [2]. Since synthesis of estrogens and androgens has been demonstrated in rat parietal cells it was suggested that the certain amounts of steroid hormones can be also synthesized in gastric mucosa [3, 4]. Relevant evidence confirming this statement came from studies concerned the expression of genes encoding steroidogenic enzymes in gastric tissues, which were responsible for in situ conversion of biologically inactive precursors into active steroids. Their deregulated expression has been shown in various neoplasms including GC [5–12]. These abnormalities can be associated with the formation of abnormal amounts of steroid hormones and thus, affect gastric carcinogenesis [9, 13].

Intracrinology

Close to 100% of active steroids in postmenopausal women and approximately 50% of androgens in adult men are produced locally in peripheral tissues [2]. However, in contrary to classical endocrine manner, the large amount of estrogens and androgens synthesized in peripheral tissues are not release into the general circulation but act locally, in the same cell where synthesis took place. To describe this local action of steroid hormones, in 1988 Labrie et al. coined new term – “intracrinology” [14]. In this process, circulating dehydroepiandrosterone (DHEA) and estrone (E1)
are metabolized to active steroid hormones by specific steroidogenic enzymes in peripheral tissues. Both, DHEA and E1, are mainly present in the blood as biologically inactive DHEA-sulfate (DHEA-S) and E1-sulfate (E1-S). DHEA-S and E1-S exhibit a long half-life, what makes them the most important reservoir of steroid precursors in the intracrine mechanism of steroid synthesis. In target tissues DHEA-S and E1-S are desulfated and then are involved in further steps of steroidogenesis [2, 5], detailed in Figure 1.

Expression of genes encoding steroidogenic enzymes in nontumoral and tumoral gastric mucosa

To date, the presence of mRNA and protein of numerous genes involved in steroidogenesis was found in nontumoral and tumoral gastric mucosa. Simultaneously, expression of some of these genes was altered in GC mucosa as compared with normal counterparts (Table 1). It was shown that the expression of steroid sulfatase (STS) at mRNA level was decreased in tumoral gastric tissues as compared with adjacent nontumoral mucosa [12]. Previous studies suggested that STS contributes to the in situ activation of E1 from E1-S in breast cancer and to mild androgen deficiency, with significantly lower circulating concentrations of DHEA and testosterone in patients with STS deficiency syndrome [15, 16]. Thus, decreased expression of STS in GC can be associated with an inhibited synthesis of estrogens and androgens due to depletion of available E1 and DHEA. Among 17β-hydroxysteroid dehydrogenases (HSD17Bs) family, mRNA of HSD17B7 as well as mRNA and protein of HSD17B1 were detected in gastric mucosa; however, there was no difference

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**Figure 1.** Steroidogenesis in peripheral tissues. Circulating dehydroepiandrosterone sulfate (DHEA-S) and estrone sulfate (E1-S), are taken up into the cell of peripheral tissues. Then, after the removal of sulfate by steroid sulfatase (STS), DHEA can be converted to 4-androstenedione (4-dione) by 3β-hydroxysteroid dehydrogenase/Δ5–4 isomerases (HSD3Bs) type 1 and 2 or to androst-5-ene-3β,17β-diol (5-diol) by the members of the family of 17β-hydroxysteroid dehydrogenases (HSD17Bs), mainly by HSD17B1 and HSD17B5. The both 4-dione and 5-diol can serve as a substrate to testosterone synthesis. Conversion of 4-dione to testosterone is catalyzed mainly by HSD17B5 whereas HSD3B1 and HSD3B2 mediate in metabolism of 5-diol. The most potent androgen, dihydrotestosterone (DHT) is produced from testosterone due to activity of 5α-reductases type 1 and 2. Estrogens are synthesized in so called "sulfatase pathway" and an "aromatase pathway". In the sulfatase pathway E1 is reduced to E2 due to the activity of HSD17B1, HSD17B5 and HSD17B7. In the aromatase pathway, E1 and E2 are synthesized by aromatase from 4-dione and testosterone respectively. Less active forms of androgens and estrogens are mainly produced by HSD17B2.
in the expression level of those genes among cancer-ous and histopathologically unchanged gastric tissues [12, 17]. On the other hand, the synthesis of E2 from E1 through HSD17B1 activity was demonstrated in GC cell lines therefore this enzyme can play a role in E2 synthesis during gastric carcinogenesis [17]. Other studies, detected an immunoreactivity of HSD17B5 in tumoral and nontumoral gastric specimens [9]. More importantly, the mRNA level of HSD17B5 (AKR1C3) was decreased in GC as compared with adjacent normal tissue [11]. Since AKR1C3 participates in the conversion of both, 4-androstenedione to testosterone and

<table>
<thead>
<tr>
<th>Gene</th>
<th>Enzyme</th>
<th>Expression in gastric</th>
<th>Method</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>STS</td>
<td>steroid sulfatase</td>
<td>Decreased mRNA expression in tumoral tissues as compared with adjacent nontumoral mucosa (60 paired samples)</td>
<td>Quantitative Real-Time PCR</td>
<td>[12]</td>
</tr>
<tr>
<td>HSD3B1</td>
<td>3β-hydroxysteroid dehydrogenase/Δ5-4 isomerase type 1</td>
<td>Decreased mRNA expression in tumoral tissues as compared with adjacent nontumoral mucosa, although very low mRNA level was observed in both type of tissues (60 paired samples)</td>
<td>Quantitative Real-Time PCR</td>
<td>[12]</td>
</tr>
<tr>
<td>HSD17B1</td>
<td>17β-hydroxysteroid dehydrogenase type 1</td>
<td>No difference in mRNA and protein expression between tumoral tissues and adjacent nontumoral mucosa (21 paired samples)</td>
<td>Quantitative Real-Time PCR and Western Blot</td>
<td>[17]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>mRNA expression was not observed in any examined histological types of mucosa (81 gastric and duodenal specimens containing normal, inflamed and neoplastic mucosa)</td>
<td>Hybridisation in situ</td>
<td>[19]</td>
</tr>
<tr>
<td>HSD17B2</td>
<td>17β-hydroxysteroid dehydrogenase type 2</td>
<td>Decreased mRNA and protein expression in tumoral tissues as compared with adjacent nontumoral mucosa (34 paired samples)</td>
<td>Quantitative Real-Time PCR and Western Blot</td>
<td>[10]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Decreased mRNA expression in most cases of malignancy as compared with nontumoral mucosa (81 gastric and duodenal specimens containing normal, inflamed and neoplastic mucosa)</td>
<td>Hybridisation in situ</td>
<td>[19]</td>
</tr>
<tr>
<td>AKR1C3</td>
<td>17β-hydroxysteroid dehydrogenase type 5</td>
<td>Decreased mRNA and non-significantly decreased protein expression in tumoral tissues as compared with adjacent nontumoral mucosa (55 paired samples)</td>
<td>Quantitative Real-Time PCR and Western Blot</td>
<td>[11]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Immunoreactivity detected in GC tissues and in the nontumoral mucosa (117 gastric cancer samples)</td>
<td>Immunohistochemistry</td>
<td>[9]</td>
</tr>
<tr>
<td>HSD17B7</td>
<td>17β-hydroxysteroid dehydrogenase type 7</td>
<td>No difference in mRNA expression in tumoral tissues as compared with adjacent nontumoral mucosa (60 paired samples)</td>
<td>Quantitative Real-Time PCR</td>
<td>[12]</td>
</tr>
<tr>
<td>CYP19</td>
<td>aromatase</td>
<td>Increased mRNA expression in tumoral gastric tissues as compared with adjacent nontumoral mucosa, although very low mRNA level was observed in both type of tissues (60 paired samples)</td>
<td>Quantitative Real-Time PCR</td>
<td>[12]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Immunoreactivity observed in 23 among 30 cases of gastric cancer and no immunoreactivity was observed in normal mucosa</td>
<td>Immunohistochemistry</td>
<td>[21]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Protein presence in gastric cancer (30 gastric cancer samples)</td>
<td>Western Blot</td>
<td>[21]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>mRNA and protein presence in tumoral tissues and adjacent nontumoral mucosa (19 paired samples)</td>
<td>Quantitative Real-Time PCR and Immunohistochemistry</td>
<td>[25]</td>
</tr>
<tr>
<td>SRD5A1</td>
<td>steroid 5α-reductase type 1</td>
<td>Immunoreactivity in 69 of 117 cases of tumoral mucosa and no observed immunoreactivity in normal mucosa</td>
<td>Immunohistochemistry</td>
<td>[9]</td>
</tr>
<tr>
<td>SRD5A2</td>
<td>steroid 5α-reductase type 2</td>
<td>Immunoreactivity in 57 of 117 cases of tumoral mucosa and no observed immunoreactivity in normal mucosa</td>
<td>Immunohistochemistry</td>
<td>[9]</td>
</tr>
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Table 1. Expression of genes involved in steroidogenesis examined in gastric
E1 to E2, its down-regulation can result in the reduc-
tion of intratissue concentration of biologically potent
steroids [18]. Furthermore, the presence of HSD17B2
mRNA was confirmed in different histological types
of gastric mucosa. Its decreased expression at both
mRNA and protein level has been observed in tumor-
al gastric specimens as compared with nontumor-
counterparts [10, 19]. The role of androgens in GC is
unclear; however, some studies suggest that testos-
terone can induce gastric cancerogenesis [20]. There-
fore, down-regulation of HSD17B2 can be associated
with increased intracellular concentration of E2 which
can be protective, but also with an increased level of
testosterone which can be noxious. In fact, an immu-
noreactivity of 5α-reductases type 1 and 2, which are
responsible for the synthesis of DHT, the most biologi-
cally potent form of androgens, was reported in gastric
carcinoma but not in the non-neoplastic gastric epi-
thelium [9].

Synthesis of androgens in peripheral tissues is
also controlled by 3β-hydroxysteroid dehydrogenase/
Δ5–4isomerase type 1 (HSD3B1). Surprisingly, stud-
ies has shown lower mRNA level of HSD3B1 in gastric
cancerous mucosa than in normal adjacent mucosa;
however, overall mRNA content of this gene was low in
both types of gastric tissues [12]. Importantly, andro-
gen can be subsequently aromatized to estrogens
by aromatase (CYP19) [2]. It was revealed that CYP19
mRNA level was increased in GC as compared with
nontumor specimens, but similarly to HSD17B2, mRNA
content of CYP19 was found to be low in both types of
examined tissues [12]. In the other studies, positive
immunoreactivity for CYP19 was demonstrated in GC,
whereas all nontumor gastric mucosa specimens
were negative for this enzyme [21]. Nevertheless, rat
models demonstrated the capability of parietal cells to
convert circulating androgens into estrogens with the
simultaneous expression of CYP19 mRNA and protein
[22–24]. Moreover, the synthesis of E2 through aromat-
ization of exogenous testosterone was demonstrated in
GC cell lines [25]. Thus, expression of CYP19 seems
to play some role in estrogen synthesis from andro-
gen in gastric mucosa.

Conclusion

Several studies confirmed that genes involved in local
steroidogenesis are expressed in normal and cancer-
ous gastric mucosa. Therefore, some amounts of ste-
roid hormones can be synthesized in these tissues.
Because the majority of examined genes were found to
be down-regulated in GC as compared with nontumor
gastric mucosa, gastric cancerogenesis can be asso-
ciated with reduced production of steroid hormones in
situ. However, the exact role of estrogens and andro-
gen in GC development and progression needs to be
further clarified. At that time, above findings could be
helpful in therapeutic approaches.

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Conflict of interest statement

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