THOUSAND WORDS ABOUT...

DOI: https://doi.org/10.20883/jms.2017.151

Intracrinology and gastric cancer

Bartosz Adam Frycz, Paweł Piotr Jagodziński

Department of Biochemistry and Molecular Biology, Poznan University of Medical Sciences, Poland

ABSTRACT

Overall incidence of gastric cancer (GC) in most populations is approximately two times higher in men than women. Therefore, steroid hormones are suspect to play a role in gastric carcinogenesis. Large amounts of steroid hormones in postmenopausal women and older men are synthesized in peripheral tissues through enzymatic conversion of blood derived precursors into active estrogens and androgens in so called, intracrine mechanism. Moreover, abnormal expression of genes encoding steroidogenic enzymes was shown in numerous malignant tumors including GC. These abnormalities can be associated with deregulated production of steroid hormones in gastric tissue and thus affect the risk of GC. For that reason this short review aims to summarize the current knowledge about the expression of genes involved in metabolism of steroid hormones in normal and malignant gastric mucosa and thus, estimate the potential of these tissues to intracrine synthesis of steroid hormones. This findings could be useful in understanding the role of above mechanism in GC and could help to find therapeutic approaches in future.

Keywords: steroidogenesis; intracrinology; gastric cancer.

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 in postmenopausal women and older men [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 neoplasm 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-sulphate (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

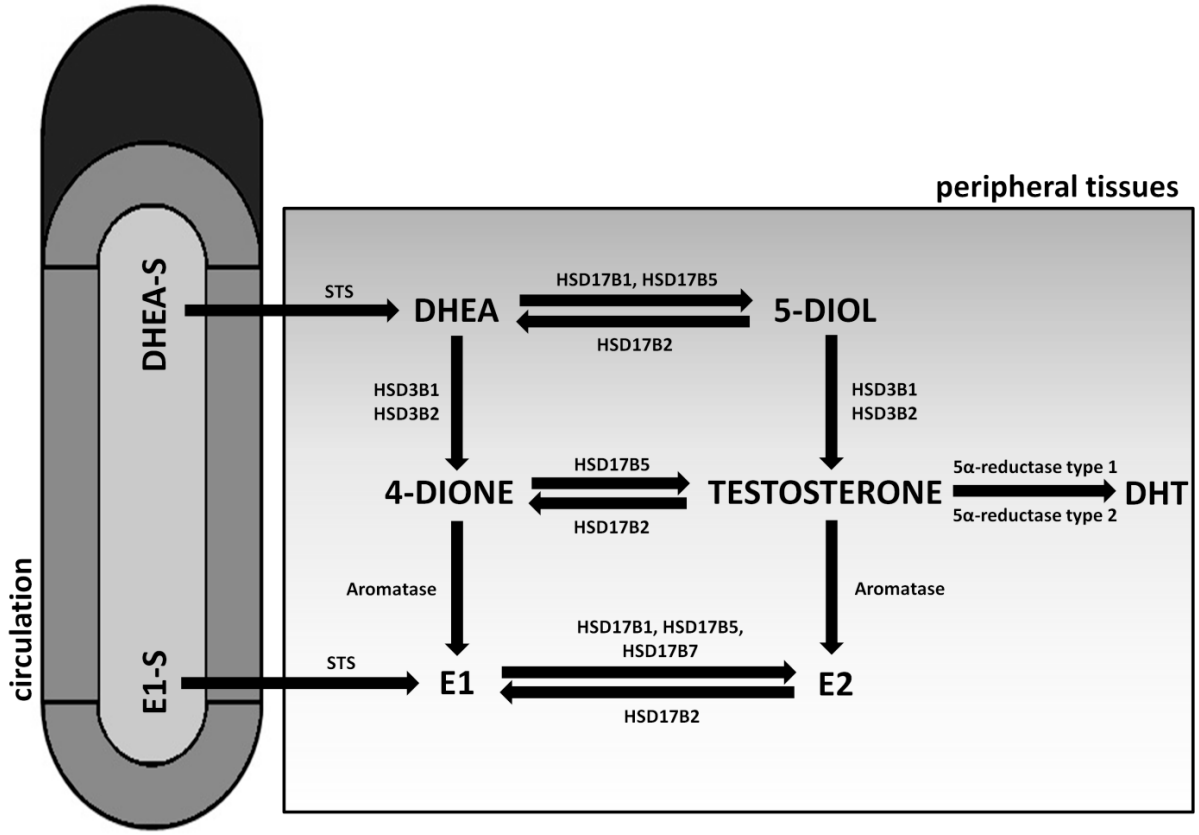

Figure 1. Steroidogenesis in peripheral tissues. Circulating dehydroepiandrosterone sulfate (DHEA-S) and estrone sulfate (E1-S), are taken up into the cell of peripheral tissues. Then, after the removal of sulfate by steroid sulfatse (STS), DHEA can be converted to 4-androstenedione (4-dione) by 3β-hydroxysteroid 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

Table 1. Expression of genes involved in steroidogenesis examined in gastric

Gene	Enzyme	Expression in gastric	Method	References
STS	steroid sulfatase	Decreased mRNA expression in tumoral tissues as compared with adjacent nontumoral mucosa (60 paired samples)	*Quantitative Real-Time PCR*	[12]
HSD3B1	3β-hydroxysteroid dehydrogenase/ Δ5–4 isomerase type 1	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)	*Quantitative Real-Time PCR*	[12]
HSD17B1	17β-hydroxysteroid dehydrogenase type 1	No difference in mRNA and protein expression between tumoral tissues and adjacent nontumoral mucosa (21 paired samples)	*Quantitative Real-Time PCR and Western Blot*	[17]
		mRNA expression was not observed in any examined histological types of mucosa (81 gastric and duodenal specimens containing normal, inflamed and neoplastic mucosa)	Hybridisation *in situ*	[19]
HSD17B2	17β-hydroxysteroid dehydrogenase type 2	Decreased mRNA and protein expression in tumoral tissues as compared with adjacent nontumoral mucosa (34 paired samples)	*Quantitative Real-Time PCR and Western Blot*	[10]
		Decreased mRNA expression in most cases of malignancy as compared with nontumoral mucosa (81 gastric and duodenal specimens containing normal, inflamed and neoplastic mucosa)	Hybridisation *in situ*	[19]
AKR1C3	17β-hydroxysteroid dehydrogenase type 5	Decreased mRNA and non-significantly decreased protein expression in tumoral tissues as compared with adjacent nontumoral mucosa (55 paired samples)	*Quantitative Real-Time PCR and Western Blot*	[11]
		Immunoreactivity detected in GC tissues and in the nontumoral mucosa (117 gastric cancer samples)	*Immunohistochemistry*	[9]
HSD17B7	17β-hydroxysteroid dehydrogenase type 7	No difference in mRNA expression in tumoral tissues as compared with adjacent nontumoral mucosa (60 paired samples)	*Quantitative Real-Time PCR*	[12]
CYP19	aromatase	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)	*Quantitative Real-Time PCR*	[12]
		Immunoreactivity observed in 23 among 30 cases of gastric cancer and no mmunoreactivity was observed in normal mucosa	*Immunohistochemistry*	[21]
		Protein presence in gastric cancer (30 gastric cancer samples)	*Western Blot*	[21]
		mRNA and protein presence in tumoral tissues and adjacent nontumoral mucosa (19 paired samples)	*Quantitative Real-Time PCR and Immunohistochemistry*	[25]
SRD5A1	steroid 5α-reductase type 1	Immunoreactivity in 69 of 117 cases of tumoral mucosa and no observed immunoreactivity in normal mucosa	*Immunohistochemistry*	[9]
SRD5A2	steroid 5α-reductase type 2	Immunoreactivity in 57 of 117 cases of tumoral mucosa and no observed immunoreactivity in normal mucosa	*Immunohistochemistry*	[9]

in the expression level of those genes among cancerous 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

E1 to E2, its down-regulation can result in the reduction 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 tumoral gastric specimens as compared with nontumoral counterparts [10, 19]. The role of androgens in GC is unclear; however, some studies suggest that testosterone can induce gastric cancerogenesis [20]. Therefore, 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 immunoreactivity of 5α-reductases type 1 and 2, which are responsible for the synthesis of DHT, the most biologically potent form of androgens, was reported in gastric carcinoma but not in the non-neoplastic gastric epithelium [9].

Synthesis of androgens in peripheral tissues is also controlled by 3β-hydroxysteroid dehydrogenase/Δ5–4isomerase type 1 (HSD3B1). Surprisingly, studies 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, androgens can be subsequently aromatized to estrogens by aromatase (CYP19) [2]. It was revealed that *CYP19* mRNA level was increased in GC as compared with nontumoral specimens, but similarly to *HSD3B1*, 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 nontumoral 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 aromatization of exogenous testosterone was demonstrated in GC cell lines [25]. Thus, expression of CYP19 seems to play some role in estrogen synthesis from androgens in gastric mucosa.

Conclusion

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

Acknowledgements

Conflict of interest statement
The authors declare no conflict of interest.

Funding sources
There are no sources of funding to declare.

References

1. Camargo MC, Goto Y, Zabaleta J, Morgan DR, Correa P, Rabkin CS. Sex hormones, hormonal interventions, and gastric cancer risk: a meta-analysis. Cancer Epidemiol Biomarkers Prev. 2012;21(1):20–38.
2. Labrie F. Extragonadal synthesis of sex steroids: intracrinology. Ann Endocrinol (Paris). 2003;64(2):95–107.
3. Ueyama T, Shirasawa N, Numazawa M, Yamada K, Shelangouski M, Ito T, Tsuruo Y. Gastric parietal cells: potent endocrine role in secreting estrogen as a possible regulator of gastro-hepatic axis. Endocrinology. 2002;143(8):3162–70.
4. Le Goascogne C, Sananès N, Eychenne B, Gouézou M, Baulieu EE, Robel P. Androgen biosynthesis in the stomach: expression of cytochrome P450 17 alpha-hydroxylase/17,20-lyase messenger ribonucleic acid and protein, and metabolism of pregnenolone and progesterone by parietal cells of the rat gastric mucosa. Endocrinology. 1995;136(4):1744–52.
5. Sasano H, Suzuki T, Nakata T, Moriya T. New development in intracrinology of breast carcinoma. Breast Cancer. 2006;13(2):129–36.
6. Mungenast F, Thalhammer T. Estrogen biosynthesis and action in ovarian cancer. Front Endocrinol (Lausanne). 2014;5:192.
7. Frycz BA, Jagodziński PP. Expressions of genes encoding steroidogenic enzymes and their role in prostate carcinogenesis. JMS. 2014;83(1):73–80.
8. Drzewiecka H, Gałęcki B, Jarmołowska-Jurczyszyn D, Kluk A, Dyszkiewicz W, Jagodziński PP. Increased expression of 17-beta-hydroxysteroid dehydrogenase type 1 in non-small cell lung cancer. Lung Cancer. 2015;87(2):107–16.
9. Nakamura Y, Shimada N, Suzuki T, Imatani A, Sekine H, Ohara S et al. In situ androgen production in human gastric carcinoma--androgen synthesizing and metabolizing enzymes. Anticancer Res. 2006;26(3A):1935–9.
10. Frycz BA, Murawa D, Borejsza-Wysocki M, Marciniak R, Murawa P, Drews M, Jagodziński PP. Expression of 17β-hydroxysteroid dehydrogenase type 2 is associated with some clinicopathological features in gastric cancer. Biomed Pharmacother. 2015;70:24–7.
11. Frycz BA, Murawa D, Borejsza-Wysocki M, Wichtowski M, Spychała A, Marciniak R et al. Transcript level of

AKR1C3 is down-regulated in gastric cancer. Biochem Cell Biol. 2016;94(2):138–46.
12. Frycz BA, Murawa D, Borejsza-Wysocki M, Wichtowski M, Spychała A, Marciniak R et al. mRNA expression of selected genes encoding steroidogenic enzymes, steroid hormone receptors and their co-regulators in gastric cancer. Oncology Letters [ahead of published]
13. Brodie A, Njar V, Macedo LF, Vasaitis TS, Sabnis G. The Coffey Lecture: steroidogenic enzyme inhibitors and hormone dependent cancer. Urol Oncol. 2009;27(1):53–63.
14. Labrie C, Belanger A, Labrie F. Androgenic activity of dehydroepiandrosterone and androstenedione in the rat ventral prostate. Endocrinology. 1988;123(3):1412–7.
15. Suzuki M, Ishida H, Shiotsu Y, Nakata T, Akinaga S, Takashima S et al. Expression level of enzymes related to in situ estrogen synthesis and clinicopathological parameters in breast cancer patients. J Steroid Biochem Mol Biol. 2009;113(3–5):195–201.
16. Idkowiak J, Taylor AE, Subtil S, O'Neil DM, Vijzelaar R, Dias RP et al. Steroid Sulfatase Deficiency and Androgen Activation Before and After Puberty. J Clin Endocrinol Metab. 2016;101(6):2545–53.
17. Frycz BA, Murawa D, Wysocki-Borejsza M, Marciniak R, Murawa P, Drews M, Jagodziński PP. Expression of 17β-hydroxysteroid dehydrogenase type 1 in gastric cancer. Biomed Pharmacother. 2013;67(7):651–7.
18. Dozmorov MG, Azzarello JT, Wren JD, Fung KM, Yang Q, Davis JS et al. Elevated AKR1C3 expression promotes prostate cancer cell survival and prostate cell-mediated endothelial cell tube formation: implications for prostate cancer progression. BMC Cancer. 2010;10:672.
19. Oduwole OO, Mäkinen JM, Isomaa VV, Karttunen TJ, Vihko PT. Sex steroid metabolism in human gastric mucosa: 17 beta-hydroxysteroid dehydrogenase type 2 in normal, inflamed and neoplastic gastric tissues. Anticancer Res. 2003;23(5A):3889–97.
20. Tian Y, Wan H, Lin Y, Xie X, Li Z, Tan G. Androgen receptor may be responsible for gender disparity in gastric cancer. Med Hypotheses. 2013;80(5):672–4.
21. Saitoh Y, Sasano H, Naganuma H, Ohtani H, Sasano N, Ohuchi A, Matsuno S. De novo expression of aromatase in gastric carcinoma. Light and electron microscopic immunohistochemical and immunoblot study. Pathol Res Pract. 1992;188(1–2):53–60.
22. Kobayashi H, Yoshida S, Sun YJ, Shirasawa N, Naito A. Postnatal development of gastric aromatase and portal venous estradiol-17β levels in male rats. J Endocrinol. 2013;218(1):117–24.
23. Kobayashi H, Yoshida S, Sun YJ, Shirasawa N, Naito A. 17β-Estradiol in the systemic circulation derives mainly from the parietal cells in cholestatic female rats. J Endocrinol Invest. 2016;39(4):389–400.
24. Ozawa M, Takahashi K, Akazawa KH, Takashima T, Nagata H, Doi H et al. PET of aromatase in gastric parietal cells using 11C-vorozole. J Nucl Med. 2011;52(12):1964–9.
25. Izawa M, Inoue M, Osaki M, Ito H, Harada T, Terakawa N, Ikeguchi M. Cytochrome P450 aromatase gene (CYP19) expression in gastric cancer. Gastric Cancer. 2008;11(2):103–10.

Acceptance for editing: 2016-12-22
Acceptance for publication: 2016-03-27

Correspondence address:
Bartosz Adam Frycz
Poznan University of Medical Sciences
Department of Biochemistry and Molecular Biology
6 Święcickiego Street, 60-781 Poznań, Poland
phone: +48 618546513
fax: +48 618546510
e-mail: bartekfrycz@gmail.com