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Erythropoietin Concomitantly with Ethinyl Estradiol can Cause Uterine and Ovarian Cancers

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Erythropoietin and Estradiol Promote the Growth of Malignancies

Erythropoietin (Epo), by binding to its receptor (EpoR), protects erythroid progenitor cells from apoptotic death and stimulates their proliferation and differentiation into hemoglobin-containing erythrocytes. In the body, the production of Epo in the kidney depends on the oxygen concentration in the circulating blood, i.e. Epo is induced by hypoxia. However, we found that Epo production is induced by estradiol (E2) more than by hypoxia in the mouse uterus [1] and that the human ovaries, uterus, and cervix can produce Epo through the expression of Epo mRNA with Epo-EpoR signaling [2]. Deprivation of Epo signaling destroyed the surgically resected specimens of ovarian, uterine and cervical cancers through anti-Epo antibody and soluble form of EpoR which can bind to Epo secreted from cancer cells in vivo in nude mice [3] and *in vitro* [4]. Twenty-four malignant human cell lines including leukemia cell lines examined expressed Epo and EpoR mRNAs with respective proteins, regardless of their origin, type, genetic characteristics, and biological properties. Furthermore, deprivation of Epo signaling in xenografts of stomach choriocarcinoma and melanoma cell lines using the EpoR antagonist, EMP9, led to the destruction of these xenografts [5]. Epo-EpoR signaling has been found in breast cancers [6,7], prostate cancers [8] and many other cancers [9].

Unrecognizable Exposure to Synthetic Estrogens can Cause Malignancies

In 1971, Herbst et al. [10] reported that diethylstilbestrol, a synthetic estrogen, acts as a transplacental carcinogen causing vaginal adenocarcinoma in females born to mothers who were prescribed the drug during their pregnancy. Since then, we have been studying the effects of prenatal exposure to ethinyl estradiol (EE2), which is the most effective synthetic estrogen and is now used as a component of oral contraceptives.

We found various effects of EE2 in mature female mice, such as cystic glandular hyperplasia of endometrium and loss of primordial follicles in the ovary [11]; and, we also detected endometriotic changes of the uterine endometrium [12]. In the testes of mature male mice, EE2 was found to cause drastic conversion of testosterone to estradiol which occurred concomitantly with the production of adenocarcinomatous lesions in the epididymis [13].

Transplacental effects of EE2 on fetal development detected at term, were hypertrophic nipples in females [14], gonadal dysgeneses such as ovotestis, intra-abdominal testes, ovarian hypoplasia [15], and Leydig cell hyperplasia in the testes [16]. Recently, we analyzed these morphological changes induced by the prenatal exposure to EE2 by qT-RT-PCR methods and found the up regulation of aromatase mRNA in the uterus and ovaries of the mice [17].

Higher Expression Rate of Aromatase mRNA in Uterine and Ovarian Cancers

Since, uterine and ovarian cancers are known to express transcripts for Epo, EpoR, aromatase, and VEGF, we measured these mRNA levels in surgically resected normal and malignant samples of patients by real-time quantitative RT-PCR analysis. No significant differences were detected between the malignant and normal samples of the average expression of these transcripts. However, the ratios of mRNA levels of aromatase to Epo, EpoR and VEGF between the malignant to normal origins showed higher levels, especially in uterine cancers (Table 1).

Another Unrecognizable Exposure Induces Hormonal Imbalance Leading to Sterility in Humans

The environmental chemicals have been reported to be important factors affecting the fertility of men and women exposed to them during their prenatal and/or neonatal period.

Exposure to p,p'-dichloro diphenyl trichloroethane (DDT) has been reported to induce precocious puberty [18] ; polycystic aromatic hydrocarbons (PAHs) that are present in tobacco smoke binds to aromatic hydrocarbons receptor (Ah receptor) in the ovary leading to apoptotic death of the fetal germ cells due to the accumulation of Bax protein in them [19,20]; polychlorinated dibenzo-p-dioxin(PCDD, PCDF, TCDD) by binding to the Ah receptor induces reduced sperm counts in adult [21]; polychlorinated biphenyl(PBS) and polyhalogenated hydrocarbons (PHAs) suppress activity of the enzyme, estrogen sulphotransferase (SULTIEI) leading to high activity of estrogen [22].

Conclusion

Taking into consideration the data that prenatal exposure to EE2 induces significantly higher aromatase expression in fetal and adult mouse testes as well as in the mature mouse uterus and ovaries, unrecognizable exposure and/or prescription of oral contraceptives (EE2) may cause uterine and ovarian cancer in females and sterility in males. Furthermore, another unrecognizable exposure to the environmental chemicals such as DDT, PAH, dioxin, PCB, and PHA, during prenatal period are reported to cause sterility in men and women due to the disruption of hormonal balance to differentiate into male and female reproductive organs.

Table 1: Average mRNA levels and their expression ratio in normal and malignant uterus and ovaries

		Average transcriptional levels*							
		Epo mRNA		EpoR mRNA		Aromatase mRNA		VEGF mRNA	
Uterus	Normal	0.39 ± 0.07 (12)		1.78 ± 0.16 (12)		0.41 ± 0.14 (12)		15.55 ± 2.35 (12)	
	Malignant	0.10 ± 0.02 (21)		1.48 ± 0.16 (21)		0.81 ± 0.30 (21)		7.74 ± 1.27 (21)	
Ovaries	Normal	3.22 ± 1.76 (5)		1.66 ± 0.50 (5)		3.21 ± 0.94 (5)		20.84 ± 8.02 (5)	
	Malignant	0.12 ± 0.03 (10)		0.82 ± 0.10 (10)		0.52 ± 0.12 (10)		5.58 ± 0.86 (10)	
		Aromatase/Epo mRNA		Aromatase/EpoR mRNA		-		Aromatase/VEGF mRNA	
		Respective ratio	Malignant to normal	Respective ratio	Malignant to normal			Respective ratio	Malignant to normal
Uterus	Normal	1.10 (12)	7.30	0.23 (10)	2.40			0.03 (10)	3.30
	Malignant	8.10 (21)		0.55 (21)				0.101 (21)	
Ovaries	Normal	1.00 (5)	4.73	1.96 (5)	0.32			0.15 (5)	0.06
	Malignant	4.73 (10)		0.63 (10)				0.01 (10)	

The number in parentheses indicates the number of samples examined.
*Relative content of each mRNA to 18S rRNA mRNA.

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