Steroids 138 (2018) 108–116

Contents lists available at ScienceDirect

Steroids

journal homepage: www.elsevier.com/locate/steroids

Estrogen matters in metastasis

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ARTICLE INFO

Keywords:
Estrogen
ERα
ERβ
Metastasis
Intravasation
Extravasation
Invasion
Anoikis
Angiogenesis

ABSTRACT

Metastatic cancer cells meet several physical, biochemical and immunological barriers before colonizing a new territory. Cancerous cells turn invasive, mobile and eventually disengage from their native niche. This is followed by their intravasation, extravasation, survival, proliferation, and colonization into distant organs. Unlike well-confined tumors, which respond favorably to anti-cancer therapeutics, metastatic tumors are life-threatening and incurable. More than 90% of cancer-related mortality is caused by metastases, hence the emphasis is now on developing the strategies to block or reverse the process of metastasis. This has ensued intensive research with a focus on the mechanisms underlying metastasis. Substantial work carried out in this direction has led to the identification of specific enzymes, proteins, cytokines, chemokines, growth factors, exosomes, miRNA and lipids, etc. as the facilitators of metastasis. Metastatic cells are exposed to a diverse array of local and systemic signals. Among these, estrogens are of great relevance. Estrogens have been strongly linked to cancers, especially of breast and uterine origin. Recent data hint that estrogens, well recognized for their role in proliferation, may have a role in metastasis also. It is proposed that influence of estrogen on metastasis may be independent of its proliferation-inducing ability. Data are emerging to suggest that estrogens have potential to modulate various events of the metastatic cascade such as local invasion, intravasation, anoikis, immune evasion, extravasation, angiogenesis and metastatic colonization. This review summarizes some of the recent advances in our knowledge on the role of estrogens in the metastatic cascade of cancerous cells.

1. Introduction

Estrogen {derived from Latin “Estrous” meaning heat or vehement desire}, a steroid hormone, plays a critical role in growth, development, and functions of the reproductive system in females. Estrone (E1), estradiol (E2, or 17β-estradiol), and estriol (E3) are three forms of physiological estrogens, derived from cholesterol and among these, E2 is the major and most potent product synthesized during estrogen biosynthesis in premenopausal females [1]. Estrogen was previously recognized for its exclusivity to females, on account of its being an ovarian product. However, it is now known that estrogen is synthesized and has functions in males too. Estrogen regulates not only the reproductive functions but also several non-reproductive functions of cardiovascular, neuronal and skeletal systems. Various tissues such as placental syncytiotrophoblast, adipose tissue, skin fibroblasts, bone, and brain synthesize estrogens from androgens [2].

In December 2003, the National Institute of Environmental Health Sciences (NIEHS), US included estrogens in its list of known carcinogens. Previous investigations reported higher incidences of cancer in women who opt for estrogen replacement therapy (HRT) to alleviate post-menopausal symptoms [Reviewed in 3]. However, a recent Women’s Health Initiative (WHI) study conducted on 5310 women receiving conjugated equine estrogens revealed no additional risk of cancer mortality, compared to women receiving placebo during a cumulative follow-up of 18 years [4]. On the other hand, observational studies indicated a reduction in the risk of colorectal cancer in postmenopausal women who had received estrogen replacement therapy [5]. In a mouse model of adenomatous polyposis coli-associated colorectal cancer also, ovariectomy led to a significant increase in the number of intestinal adenomas. These animals on treatment with E2 showed a remarkable reduction in the number of intestinal adenomas [6]. Estrogens are also used as therapeutics for human breast and prostate cancers [7–9]. Thus, estrogen has paradoxical functions as it acts as a carcinogen and also as an anti-cancer agent. This dualism in estrogen function is believed to result from dose-dependent effects, the existence of different estrogen receptors with multiple isoforms and location-dependent roles.

Estrogen mediates physiological effects by binding to specific estrogen receptors; ERα and ERβ, encoded by different genes. Alternate splicing events generate at least 3 isoforms of ERα and five isoforms of

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https://doi.org/10.1016/j.steroids.2018.07.006
Received 13 September 2017; Received in revised form 12 July 2018; Accepted 16 July 2018
Available online 20 July 2018
0039-128X/

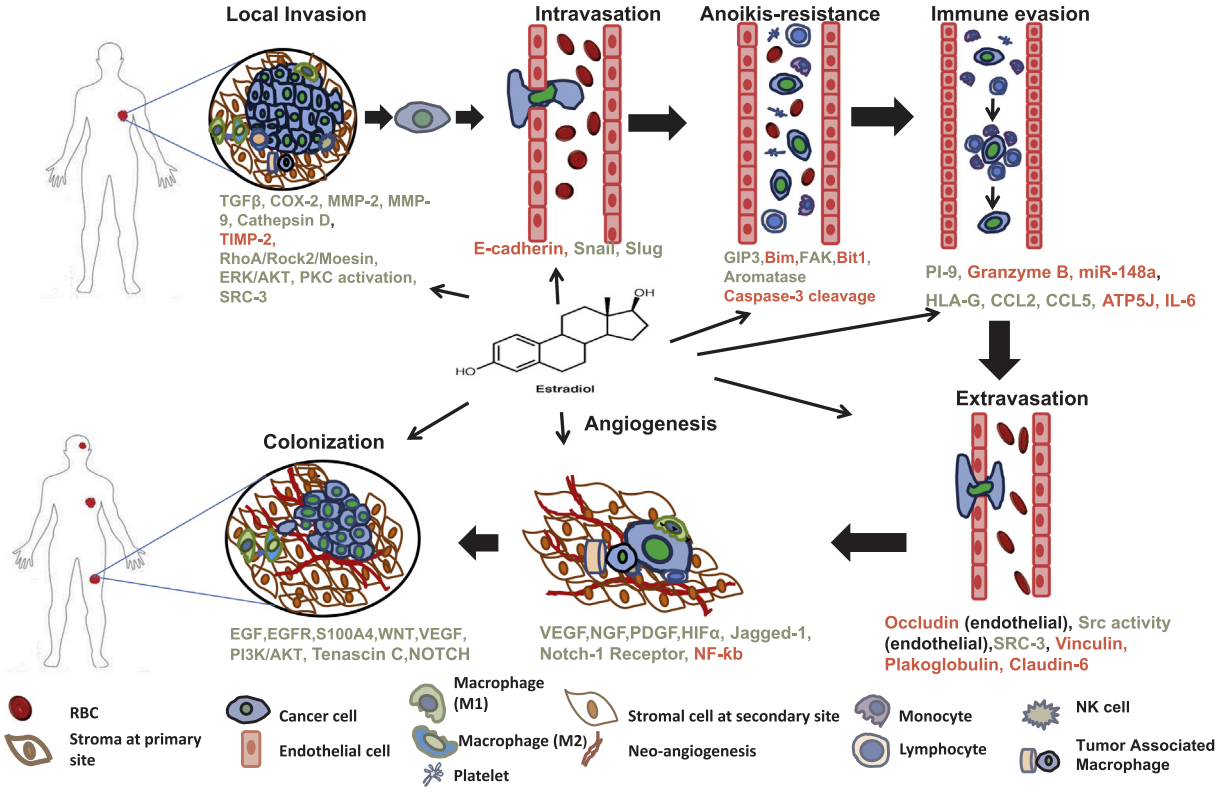

Fig. 1. 17β-Estradiol regulated factors known to be of relevance in different steps of the metastatic cascade-Local Invasion, Intravasation, Survival in circulation – Anoikis, Immune Evasion, Extravasation, Angiogenesis and Metastatic colonization. Factors upregulated or pathways activated in response to estrogenic influences are shown in green, whereas those downregulated or repressed are shown in red.

ERβ. These receptors behave differently in response to different ligands, due to the dissimilarities in their activation function domain. ERα and ERβ recruit different coactivators/cofactors and bind to them with variable affinities. Localization of the receptor isoforms and their levels vary among different tissue types [10]. This partially explains cell or tissue-context dependent functions of estrogens. Further, it is proposed that only bad estrogens i.e. estrogens whose metabolite generate oxygen radicals and cause DNA damage, are carcinogenic [11]. This was evidenced by experiments demonstrating the development of kidney cancer in hamsters implanted with E2 pellets but not in those implanted with 17 alpha-ethinylestradiol (EE), a synthetic form of estrogen. Although both estrogens led to proliferation, unlike E2, EE was poorly metabolized and did not produce free radicals [11].

It is conventionally believed that the metastasis is a late stage event in cancer progression, although some studies refute this notion. These studies have shown that cells from early neoplastic lesions have an ability to disseminate from their site of origin to other organs; however, it remains unsettled whether metastasis is caused by or results independently of cancer-driving events. Experimental evidences have shown that the metastatic process is highly inefficient as only ~0.01% of cancer cells released into the circulation develop into metastatic foci [12]. It is not yet clear which step of the metastasis cascade is the most rate-limiting step. Melanoma cells injected into chick embryo chorioallantoic membrane were found to survive in the microcirculation and extravasate efficiently [13]. Luzzi et al. investigated the multistep nature of metastatic inefficiency in a mouse liver model, by quantifying the number of intra-portally injected B16F1 melanoma cells, which survive, extravasate, micro metastasize and develop into macroscopic tumors. It was found that > 80% of the injected cells survived and had extravasated by day 3. However, only a few extravasated cells formed micro-metastases by day 3 and of these, very few micrometastases formed macroscopic tumors. This was suggestive of a possibility that extravasation and the steps that precede it are probably not the rate-limiting steps in the cascade of metastasis [14]. It is likely that the micro-environment constituted by local signals and tissue- specific immunity at non-native sites pose formidable challenge to survival of disseminated tumor cells.

Efforts have also been made to discern whether metastasis is a continuum of tumorigenicity or occurs independently of tumor-causing events [15]. For this, mammary cells were engineered to express an oncogene in a doxycycline-dependent mammary-specific manner [15]. Intravenously injected normal mammary cells were found to be lodged in the lungs. These cells grew slowly in the lungs and became metastatic malignancies, only when oncogenes were turned on. These observations indicated that, in the absence of an active oncogene, dissociated cells from an untransformed mouse mammary gland can establish residence in the ectopic environment of the lung, grow slowly, and remain clinically undetectable. The study demonstrated that activated oncogenes and cellular transformation were not required for the steps subsequent to intravasation such as survival in circulation, anoikis, and extravasation. This indirectly supports the concept that cells from small cancers may spread to distant sites early in tumorigenesis and account for dormancy and late relapse in certain cancers [16,17]. Further, it was demonstrated that ras-transformed and control fibroblasts extravasate to the same extent, again suggesting that extravasation is independent of metastatic ability [18]. Collectively, these studies suggest that the primary determinants of metastatic inefficiency are post-extravasation survival and growth of cells. Emerging evidences indicate that estrogen influences not only post-extravasation survival and growth but also the steps that precede these two events and tip the scale in favor of metastasis [19–25].

Studies conducted using an experimental model of breast cancer metastasis demonstrated the facilitatory effect of E2 on metastasis of ER-negative breast cancer cells to the lung in ovariectomized mice [22]. E2 enhanced metastatic tumor colony formation and increased the size of tumor nodules in the lungs. This was partially attributed to E2-