The oestrogen-dependent regulation of cell behaviour is realised by stimulation of specific oestrogen receptors. The classical oestrogen receptors ERα and ERβ are transcription factors, and they modulate expression of hormonally regulated genes, while the third one, GPER, is thought to be responsible for the observed rapid, non-genomic cellular response. Oestrogen dependency is attributed to a number of cancers, including breast, ovarian and endometrial cancer; however, there is still growing evidence that melanoma should also be cited as a hormonally dependent tumour. This comes from the observations of gender-related differences in melanoma progression and reports concerning the history of the malignant course of melanomas during pregnancy. Although, the observations of oestrogen regulation of melanoma progression are controversial, the effect of oestrogen should not be neglected, as the skin possesses its own hormonal microenvironment. This aspect of melanoma progression should be taken under careful consideration as it may offer new therapeutic possibilities.

Key words: melanoma, oestrogen, oestrogen receptor α, oestrogen receptor β, GPER.

Is oestrogen an important player in melanoma progression?

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Introduction

The biological effects of oestrogen are mediated by its binding to, and activation of, the oestrogen receptors ERα and ERβ [1, 2]. The observed activation of the G protein-coupled oestrogen receptor (GPER) after oestrogen stimulation implies that it could be the third oestrogen receptor [3–5]. ERα and ERβ are transcription factors interacting with the oestrogen response elements (EREs) located within the promoter regions of hormonally regulated genes (Fig. 1). They participate in the formation of a multi-protein complex there, and as a result, they regulate the transcription process [6–8]. Both these receptors possess multi-domain structures and are composed of a highly conserved DNA-binding domain, a ligand-binding domain and two transcriptional activation functions AF1 and AF2. The DNA-binding domain is involved in recognition and binding of DNA and is located in the centre of the receptor protein, while the ligand-binding domain, engaged in receptor-ligand interactions, is located in the COOH terminal. The NH_2-terminal domain is the most variable domain regarding its sequence and length. This is also the region where the AF1 is located, while the AF2 is found in the COOH terminal. AF1 is constitutively activated and AF2 is hormone-dependent [9, 10]. ERα and ERβ are soluble receptors that can shuttle between the cytoplasm and the nucleus, but they are found largely in the nucleus [11–13]. These receptors are products of distinct genes located on different chromosomes. Both types are synthesised in multiple splice variants; however, the biological activity of those variants has not been fully understood yet. For example, the shorter ERα isoforms lacking the NH_2-terminal AF-1, named hERα-46 and hERα-36, have been isolated from different cell lines [14] but not from tissues. Their role in regulation of oestrogen effects *in vivo* is still unknown, although they represent an interesting research tool *in vitro* because they are able to heterodimerise with the full-length ERα, leading to inhibition of AF-1. It is also postulated that they can localise to plasma membrane, and therefore they can be responsible for the rapid non-genomic oestrogen effects [15–18]. The third possible oestrogen receptor, GPER, shows many of the expected characteristics of a membrane oestrogen receptor. According to study results suggesting the constitutive internalisation of plasma membrane GPER [19, 20], its localisation seems to be mostly intracellular [4, 21]. It belongs to the G protein-coupled receptor (GPCR) with seven transmembrane domains. Its activation leads to the generation of cyclic AMP (cAMP), and it is thought to be responsible for the rapid oestrogen-mediated activation of Src-dependent signalling pathway leading to extracellular signal-regulated kinases (ERKs) activation [22–25]. There are some results suggesting that this signalling pathway activation is an effect of GPCR crosstalk with epidermal growth factor receptor (EGFR) [26], insulin-like growth factor receptor (IGFR) [27] and α5β1 integrin [28] (Fig. 1). The potential role of insulin-like growth factor-1 (IGF-1) in the regulation of GPER expression was evaluated by de Marco *et al*. [29]. The GPER association with non-genomic oestrogen action has been postulated for more than 10 years, but it
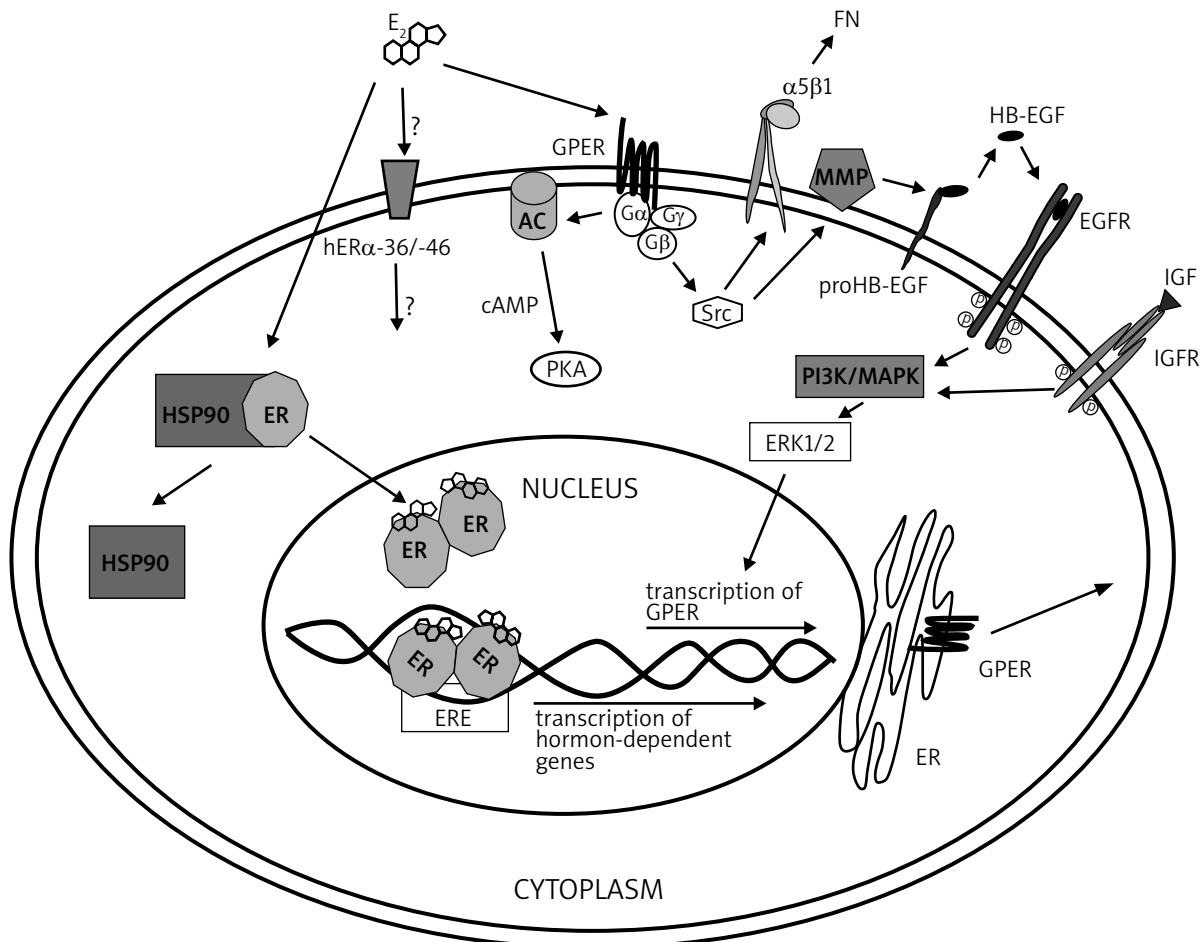
α5β1 – integrin receptor, AC – adenyl cyclase, EGFR – epidermal growth factor receptor, ER – endoplasmic reticulum, ER – oestrogen receptor (α and β), ERE – oestrogen response element, ERK1/2 – extracellular signal-regulated kinases 1/2, FN – fibronectin, GPER – G protein-coupled oestrogen receptor, HB-EGF – heparin-binding epidermal growth factor-like growth factor, HSP90 – heat shock protein 90, IGF – insulin-like growth factor, IGFR-insulin-like growth factor receptor, MAPK – mitogen-activated protein kinase, MMP – matrix metalloproteinase, PI3K – phosphoinositide 3-kinase, PKA – protein kinase A

Fig. 1. The mechanism of oestrogen action. The binding of E2 to the classical ERα or ERβ receptors leads to transcription of hormone-dependent genes. The third possible ER, GPER, is a membrane receptor, which is suggested to be responsible for non-genomic E2 action. Activated GPER triggers the clustering of α5β1 integrins, which in turn leads to the assembly of fibronectin matrix. Oestrogen action via GPER is enhanced by the presence of the IGFR-ligand complex, which results in stimulation of the GPER gene transcription. The GPER activation promotes also transactivation of EGFR, resulting in activation of signalling pathway, also leading to GPER gene transcription. Another possible way of E2 action is through hERα-36/-46, which are shorter isoforms of ERα localised in plasma membrane. Their function is not yet fully understood

is still controversial, and there are still suggestions that it does not act as an oestrogen receptor at all [30]. However, the previously suggested hypothesis that GPER and ER act in concert in some signal transduction pathways has not been totally excluded [21].

Oestrogen in melanoma progression

Although it is commonly accepted that oestrogen regulates the growth and differentiation of normal and neoplastic tissues, including breast, ovarian and endometrial tumours [31], there is growing evidence of its influence on melanoma progression as well. There are case reports showing a poor prognosis for women in whom melanoma has developed during pregnancy [32, 33] and clinical observations demonstrating that women with melanoma have better prognosis than men [34]. There are also preclinical data showing that oestrogen and its metabolites

may influence the course of melanoma progression [35, 36]. Nevertheless, observations of the influence of oestrogen on melanoma cells are controversial.

Melanomas originate from melanocytes, melanin-producing cells, found in the deep layer of the epidermis [37] and are considered as highly malignant tumours with an aggressive nature manifesting in the potential for early disease dissemination [38], which may come from very small tumour masses [39]. However, the formation of metastases in melanoma stage I and II is rarely observed. The early detection of neoplastic changes (in stage I and II) based on mole evaluation by ABCDE criteria (Asymmetry in shape, Border irregularities, Colour heterogeneity, Diameter > 6 mm and Evolution [history of morphologic changes of the lesion] [40]) significantly improve the patient survival rate. Localised lesions in the early stages are usually curable by surgical resection. Increased lesion thickness and the pres-

ence of metastases both in regional lymph nodes or distant tissues are poor prognostic indicators [41, 42]. A large number of risk factors that influence melanoma incidence and mortality rates have already been recognised. These factors are generally subdivided into two groups: genetic and environmental, which closely interact with each other [40, 42, 43].

An interesting aspect of melanoma progression, i.e. gender-related influence, has been addressed by many authors since the late 1960s [44]. Generally, it has been suggested that the disease develops more rapidly in men than in women, and that women have more favourable prognostic tumour characteristics than men [45–53]; however, geographical diversity in gender-related melanoma behaviour has also been observed [54]. There have also been studies analysing the presence of satellite and in-transit metastasis in male and female patients with cutaneous melanomas. For example, one of them, published by Meier et al. [39], showed the difference in frequencies of satellite and in-transit metastases between men (16.7%) and women (26.4%). Meier et al. [39] also observed that more frequently in men than in women the regional lymph nodes were the main sites of metastases. This observation was consistent with previous reports showing a stronger tendency in men towards tumour progression, from the stage of the primary tumour into the regional lymph nodes metastases [39]. Such gender-related tendencies in melanoma progression are thought to be influenced by endocrine status. Because skin has its own capacity to produce steroids, including oestrogen, its subjection to sex hormones should not be underestimated. Consequently, it was postulated by de Giorgi et al. [55] that melanomas should be at least cited among hormone-related neoplasms. These observations are also supported by analysis of oestrogen receptor (ER) expression in melanomas. It has been shown that ER expression is diverse between the tumour lesion and the healthy skin surrounding them. Moreover, a statistically significant difference in the mean oestrogen receptor (ER) concentrations in male versus female origin melanomas was found [56]. However, such reports are in contradiction with earlier studies indicating that the incidence of melanomas with detectable ER (refers to ERα – primarily discovered ER) is low, suggesting that the potential clinical usefulness of the ER assays in melanoma might be limited [57]. However, this was stated before the discovery of the second oestrogen receptor – ERβ.

ERβ has been shown potentially to have a suppressive effect in a variety of human tumours, such as breast, prostate, colon and ovarian cancers [58]. ERβ is suggested to have a protective function against tumour formation because it reduces uncontrolled cell proliferation by increasing apoptotic activity [34, 59]. Studies of melanoma cells have led to the conclusion that ERβ expression is altered in relation to the increasing depth of their invasion and to the diversified specificity of the tumour microenvironment [60]. These observations were further confirmed by de Giorgi et al. [61]. Based on the analysis of a small group of patients (14 patients, including 2 melanocytic nevi), they showed markedly decreased expression of ERβ in the metastatic phase of the melanoma. Moreover, it has been reported that melanoma tumours form patients suffering from lymph node metastases possessed lower expression of ERβ compared with surrounding normal skin [61]. Recently published results of a study of 66 patients with melanoma have also confirmed previous observations and have shown that increased Breslow thickness was inversely associated with lower ERβ expression in malignant melanoma tumours, compared to the adjacent healthy skin. In accordance with these findings, observations of gender-related metastasis formation have shown greater ERβ expression in women than men [62]. The reports of predominant expression of ERβ in melanoma cells have been independently confirmed by the immunohistochemistry analysis made by Ohata et al. [63], which revealed that melanocytes of melanocytic nevi and malignant melanoma cells express ERβ but not ERα. Interestingly, it has been suggested by those authors that ERβ cannot be used as a marker of melanoma progression. Ohata et al. [63] ascertained that the intensity of staining for ERβ, reflecting its level of expression, is not influenced by sex or by the serum levels of oestrogen, and it is very similar regardless of the age of female patients (ranging from 1 to 79 years) [63].

Some assumptions of the linkage between hormonal stimulation and ER expression in melanomas have been based on reports concerning melanoma development during pregnancy. In 1998 Grin et al. [64] published their critical review gathering information on controlled clinical trials assessing the effect of pregnancy on the prognosis of melanomas, and epidemiological data evaluating the risk of melanoma after exposure to oral contraceptives and hormonal replacement therapy. They concluded that pregnancy before, during or after the diagnosis of melanoma did not appear to influence 5-year survival rates. In their opinion, exposure to oral contraceptives and hormonal replacement therapy also did not appear to increase the risk of melanoma [64] as was observed in the case of other hormone-dependent cancers such as breast, ovarian, endometrial or prostate [65]. Since 1998, several reports revealing significant decreases in ERβ immunoreactivity in congenital nevi, in comparison to normal tissue and dysplastic nevi from pregnant women, have been published. All of them have suggested that nevi possess the capacity to be oestrogen-responsive. It was concluded that pregnancy and degree of atypia were associated with enhanced ERβ expression, with the exception of congenital nevi, in which the expression lowered [66]. Parallel observations have been made by Nading et al. [67] in the case of a young woman with large congenital nevi. Biopsy sample showed a decrease in nuclear staining for ERβ. It has been postulated that ERβ may have a suppressant effect in melanomas [67]. The use of oral contraceptives and hormonal replacement therapy and their association with the Breslow thickness of cutaneous melanomas has also been continuously analysed since the publication by Grin et al. [64]. Koomen et al. [68] showed that there is no such statistically significant association; however, decreased Breslow thickness among women using oestrogen, especially among older women, has not been excluded [68]. The results of Tang et al. [69] also failed to support the role of menopausal hormone therapy in the development

of non-melanoma skin cancer or melanomas in postmenopausal women. Nevertheless, ERβ was suggested as a useful prognostic marker for neoplasia and prognosis in cutaneous malignant melanoma.

Summary

In conclusion, it should be taken into consideration that, despite the fact that there is a great deal of contradiction in the results concerning the role of oestrogen in the course of melanomas, there is still growing clinical and preclinical evidence suggesting that oestrogen stimulation does have an influence on melanoma cells and may regulate their metastatic progression. Some new aspects of this problem are still being addressed by a number of researchers. Gathering those results will give a new picture of melanoma cell susceptibility to microenvironment agents. It is well known that melanomas represent an important public health problem in terms of morbidity and mortality. Therefore, efforts should be undertaken aimed at both primary prevention (risk reduction) and secondary prevention (early detection, which is critical to improve the clinical outcome of this disease) [70]. The growing focus on the role of oestrogen in melanoma progression is associated with the fact that there are still no effective and satisfying treatments for melanoma tumours. Despite the large number of agents studied in advanced melanoma [71–73], the therapy standards have remained almost unchanged and outcomes continue to be poor [74, 75]. For this reason, looking for new aspects of melanoma cell progression may serve as a starting point for finding novel methods of treatment.

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