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Editorial

Progesterone in Breast Cancer Angiogenesis

Monica C. Botelho[1,2,3]*, Raquel Soares[3,4] and Helena Alves[1]

[1]*Unit of Health Promotion and Chronic Diseases, National Institute of Health (INSA), Portugal*
[2] *IPATIMUP, Institute of Pathology and Molecular Immunology, University of Porto, Portugal*
[3]*I3S, Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Portugal*
[4]*Department of Biochemistry, University of Porto, Portugal*

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***Corresponding author**

Mónica C. Botelho, INSA - National Institute of Health Dr. Ricardo Jorge, Porto, Portugal, Email: monicabotelho@hotmail.com

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Abstract

The involvement of steroid hormones in breast carcinogenesis is well established. Recent evidence suggests that angiogenesis can be regulated by hormones. Both oestrogen and progesterone have been implicated in the angiogenic process of hormone-dependent cancers, such as breast cancer. Vascular Endothelial Growth Factor (VEGF) is a growth factor involved in angiogenesis in breast cancer that is up-regulated by estrogens. In our study we evaluated the role of progesterone in the expression of this angiogenic growth factor commonly up-regulated in breast cancer. Our findings indicate that progesterone activates an angiogenic pathway involving VEGF stimulation. The elucidation of specific angiogenic pathways promoted by progesterone can raise new therapeutic targets at least in a subset of breast cancers responsive to progesterone.

Our group has been involved in the study of breast carcinogenesis [1]. Angiogenesis, the formation of new blood vessels from pre-existing ones, encompasses a complex multistep process involving extracellular matrix degradation, endothelial cell proliferation, migration, differentiation, alignment of migrating cell for tubular formation and anatomises [2,3]. Active angiogenesis is required for pathologic processes such as inflammation and tumour growth. At exception is the female reproductive organs, in which angiogenesis is essential for tissue cyclic remodelling, occurring under the control of oestrogen and progesterone. Steroid hormones are known to play key roles in breast cancer [4] and several studies suggest that both oestrogen and progesterone might be involved in angiogenesis [5,6,7,8]. One of the genes that are up-regulated by oestrogen-Estrogens Receptor complex is Vascular Endothelial Growth Factor (VEGF) [9]. VEGF is directly involved in angiogenesis since it induces endothelial cell proliferation and permeability and is up-regulated in several tumour types [10]. Although different stimuli have been described to induce VEGF expression and activity, there are few reports on the involvement of progesterone in VEGF expression. Hyder SM et al reported that progesterone stimulated the expression of VEGF in T47D human breast cancer cell line [8]. Chennazhi KP and Nayak NR on the other hand, have observed an up regulation of VEGFR1 with progesterone withdrawal in stromal cells of the endometrium, implying that progesterone might down-regulate VEGF signalling pathway in endometrial stromal cells [11]. Studying progesterone modulators in endometrial fibroblasts and epithelial cells, Classen-Linke I et al observed that the pharmacological effects of these agents could be cell specific [6]. VEGF over expression has been reported in several angiogenic-dependent processes, such as psoriasis and wound healing [12]. Altogether these data suggest that progesterone might play a relevant role in angiogenesis, though, the exact pathway is still unknown.

Steroid hormones are known to regulate the expression of growth factors and growth factor receptors in breast cancer. Angiogenesis, on the other hand, is a complex multistep pathway that requires the presence of several cytokines and growth factors [3]. Several growth factors playing roles in angiogenesis have been shown to be activated by estrogens [2,3,9]. However, little is known regarding the implication of progesterone in angiogenesis. Our group has previously shown that platelet-derived growth factor (PDGF)-A is one of the progesterone target genes on breast cancer MCF7 and T47D cells [7]. Tumour-secreted PDGF-A is known to result in VEGF-producing fibroblast recruitment [13], reinforcing the complex interaction between tumour cells and distinct host cells through growth factors. Therefore, we focused our work on VEGF, an angiogenic growth factor that is strongly implicated in breast carcinogenesis. VEGF is a potent angiogenic factor, frequently over expressed in tumour cells. It binds to one of three VEGF receptors (VEGFR1, VEGFR2, VEGFR3) which exhibit tyrosine kinase activity, thus activating a signalling transduction pathway involved in migration, proliferation and survival of endothelial cells (EC) [14]. Although VEGF pathway was primarily identified in EC, increasing evidence indicates that VEGF can be acting in tumour cells as well [10]. The presence of VEGF receptors have been identified in several tumour cells [15]. Four different isoforms have been described in tumours by alternative splicing of VEGF gene: VEGF121, VEGF165, VEGF189, and VEGF206. The former two isoforms are efficiently

secreted and stimulate cell proliferation. In contrast, the latter two isoforms (189 and 206) are generally cell-associated and linked to vascular permeability [16]. Therefore, VEGF can either be involved in paracrine or in autocrine pathways. In our study MCF7 cell culture expressed predominantly VEGF121 isoform, after progesterone stimulation, indicating a paracrine pathway for this secreted growth factor. Accordingly, other studies [15] showed that VEGF 121 isoform is the most frequently produced by tumour cells and is required for the initial stages of tumorigenesis. Our findings that progesterone potentiates VEGF 121 expression in MCF7 cells suggest that this hormone is likely to be involved in the early stages of tumorigenesis.

Our results illustrate the role of progesterone in angiogenesis, through the activation of VEGF expression. Angiogenesis is a very complex process, involving several independent pathways. It is likely that many stimuli can lead to the activation of VEGF by different pathways.

In conclusion, this study provides further evidence that progesterone is mediating tumorigenesis in breast cancer, emphasising the role of this hormone in promoting the angiogenic phenotype. Clarifying the role of progesterone in angiogenesis might be useful to define new therapeutic strategies, at least for a specific subset of tumours that respond to progesterone.

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