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COMMENTARY

Clinical Outcomes in Breast Cancer: Innovations and Ideas Commentary on "Expression of CDK13 was Associated with Clinical Outcomes and Expression of HIF-1 and Beclin1 in Breast Cancer Patients"

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The oncogenes underlying the development of breast cancer are not fully understood and careful and rigorous research is still necessary in this area. Before considering the role of these molecules in the pathophysiology of breast cancer, as proposed by Lu et al. [1], it is necessary to outline some aspects of the molecules involved:

CDK13

CDK13 phosphorylates the C-terminal end of RNA polymerase type II in order to stop gene transcription from DNA. Its role is pivotal in the regulation of cellular development. Mutations in the gene encoding for this protein result in CDK13-related disorder, also known as *congenital heart defects, dysmorphic facial features and intellectual developmental disorder (CHDFIDD)*, which was recently defined nosologically [2].

This protein in physiological conditions is expressed ubiquitously at low levels, with higher levels in the gastrointestinal tract, kidney, bladder and testicle. In physiological breast tissue, the amount of CDK13 normally found is minimal, often not detectable.

Several studies have suggested a role of this molecule in the pathological progression [3] and in the prognostic stratification of hepatocarcinoma [4], as well as in the treatment of ovarian cancer [5]; indications that it may have a role in the oncological development of breast cancer are concrete, but still to be verified.

HIF-1alpha

The role of HIF-1alpha in oncogenesis is widely demonstrated and already studies back in the early 2000s suggested that this subunit of the HIF-1 heterodimer was involved in the development of a large number of malignancies [6].

Consideration should be given to the significance of the work of William G. Kaelin Jr, Sir Peter J. Ratcliffe and Gregg L. Semenza, awarded the Nobel Prize for Medicine in 2019 for their studies into the role of HIF-1alpha in the cellular response to hypoxia and its implications in the field of carcinogenesis.

In hypoxic environment, the alpha subunit of HIF1 binds with the beta subunit in the nucleus, forming a heterodimer that by binding to the HRE gene results in metabolic and replicative activation, promoting angiogenesis (through VEGF), erythropoiesis and glycolysis. It is no coincidence that in breast cancer, as in several other types of cancer, this molecule is over-expressed.

Beclin1

The BECN1 gene encodes for the beclin1 protein, which, by interacting with bcl2 and Pl3ks, plays a key role in regulating apoptotic processes. Other studies have suggested that low levels of this protein might be a negative predictive factor in oncological and neurodegenerative diseases.

Conversely, an overexpression of this protein has been shown to result in less aggressive malignancies and its overexpression has been hypothesized as a therapeutic target in various oncological conditions [7].

Furthermore, an alteration in autophagic processes has been hypothesized to result in pathological conditions such as schizophrenia [8].

In view of the aforementioned definition of the role in cellular processes of the molecules involved in this study by Lu et al. [1], we should now consider their specific role in the pathophysiology of breast cancer.

For this purpose, a distinction has to be established between the action of beclin1 and HIF-1alpha, whose role in the development of breast cancer has already been hypothesized and partially proven [9–11]; and the role of CDK13, for which there is very limited evidence. Noteworthy amongst such studies is the article by Quereda et al. in which the therapeutic role of CDK12-13 inhibitors is explored [12].

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In recent years, many therapeutic targets have been identified for the treatment of breast cancer, such as anti-CDK4-6 (palbociclib, abemaciclib, ribociclib) in target-therapy. The research in this field is intense, and the correlations established by Lu et al. [1] are a starting point for further enquiry [13,14].

Also of interest is the investigation of a correlation, positive or negative, between the three molecules studied; although the correlation between causes and manifestations are neither clarified nor perfectly hypothesized at this stage. Lastly, it is worth highlighting how the expression of this molecule, especially CDK13, may represent a possible future.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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