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Commentary

Rasal2, highlighting the importance of phosphorylation on function in tumour development

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Breast cancer is the most common type of cancer in women worldwide, it is estimated that its incidence will exceed 20 million new cases in 2030 [1,2]. Moreover, breast cancer is the leading cause of death due to malignancies in women, exceeding 500,000 cases annually, with about 75−85% of the cases being ER-positive; while 10−20% have a triple negative breast cancer (TNBC) phenotype [1,2].

The levels of expression or absence of specific receptors on the tumour cell leads to the generation of characteristic phenotypes, which consequently will respond differently to specific treatments [3]. Moreover, the function of a specific protein/enzyme is regulated through post-translational modifications, with phosphorylation being an important event linked to signal transduction [4]. Rasal2 is a member of the RAS GTPase-activating protein (RAS-GAP) family that inhibits RAS signalling by favoring the hydrolysis of GTP to GDP [5]. Initially, Rasal2 was believed to be a tumour suppressor given its intrinsic GAP function; a vision that was supported by different experimental evidence [5,6]. It has been shown that low levels of Rasal2 protein expression are associated with recurrence, metastasis and poor prognosis in patients with luminal B breast cancer [7]. Additionally, in breast cancer patients with metastases a low expression of Rasal2 was observed related to promoter hypermethylation [7]. These data strongly indicated the role of Rasal2 as a tumour suppressor. However, new experimental data indicated that the function of Rasal2 may be more complicated and warranted discussion by the scientific community. In 2014, Min Feng and colleagues [8] evaluated the expression of Rasal2 in a particular type of highly aggressive breast cancer, triple negative breast cancer (TNBC). They demonstrated that Rasal2 (mRNA and protein) expression levels are elevated in tumour specimens derived from TNBC or ER-negative tumours [8]. Additionally the researchers observed an overexpression of Rasal2 in metastatic nodules compared to the primary tumour samples and demonstrated that this was associated with poor disease outcome and tumour recurrence [8]. These data indicated that the role of Rasal2 in breast cancer progression depended on the cellular context and breast cancer phenotype (luminal or TNBC), however, there was no evidence that post-translational modifications modulated Rasal2 function.

In their article in *EBioMedicine*, Xuan Wang and colleagues [9] describe Rasal2 in tumour progression, with emphasis on Rasal2 phosphorylation levels as a crucial determinant of function. To determine whether Rasal2 phosphorylation modulates its function in breast cancer, the authors focused on phosphorylation of Rasal2 in serine-237 (S237, p-Rasal2) and they demonstrated that phosphorylation levels were high in ER-negative mammary tumour cells, compared to ER-positive cells, both in breast cancer cell lines lysates and human breast cancer specimens [9]. These results strongly indicate that p-Rasal2 level is a determining factor in tumour progression and that it is highly expressed in aggressive breast cancer and with poor prognosis. The group then decided to evaluate whether Rasal2 (and p-Rasal2) could be secreted as a cargo molecule in exosomes, extracellular vesicles that mediate intercellular communication [10]. Their experiments confirm that p-Rasal2 can be secreted through exosomes, and that breast cancer cells that up-take the exosomes show an increase in growth, proliferation, migration, invasion and metastasis [9]. Importantly, this work demonstrates that the function of Rasal2 depends on the level of phosphorylation at S237, and that this can be secreted into exosomes and modulate phenomena associated with tumour development.

In summary, the modulation of Rasal2 phosphorylation levels can be a promising strategy in the inhibition of cancer progression and it is crucial to evaluate the signalling pathways involved in this phenomenon. Moreover, the evaluation of p-Rasal2 through liquid biopsies may be interesting to determine its prognostic value in patients with TNBC.

Declaration of competing interest

The author declares no conflict of interest.

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