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Vav1 down-modulates activation and/or expression of specific Akt isoforms in invasive breast cancer

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Targeting different members of the Akt pathways is a promising therapeutic chance in solid tumors including breast cancer. The variable expression levels of Akt isoforms with opposite effects on tumor growth and metastasis, however, makes it difficult to select the inhibitors to be used for specific breast tumor subtypes [1]. By using in vitro and in vivo models, we demonstrated that Vav1, ectopically expressed in cells derived from invasive breast tumors [2], in which it shows a peculiar localization inside the nucleus [3], down-modulates Akt acting at expression and/or activation levels depending on tumor subtype. The decreased p-Akt1 (Ser473) levels, which are a common effect of Vav1 up-modulation, suggest that in breast tumor derived cells and independently of their phenotype, Vav1 interferes with signaling pathways ended to specifically recruit Akt1. We also found that, only in ER negative cell lines, the silencing of Vav1 induced the expression but not the activation of Akt2. Finally, a retrospective analysis of early invasive breast tumors allowed to establish the prognostic significance of the p-Akt/Vav1 relationship. Remerkably, low Vav1 levels negatively influence the follow-up of patients with low p-Akt in their primary tumors and subjected to adjuvant chemotherapy. As the use of specific or pan-Akt inhibitors may not be sufficient or may even be detrimental, to increase the levels of Vav1 could be a new approach to improve breast cancer outcomes. This might be particularly relevant for tumors with a triple negative phenotype, for which effective target-based therapies are not currently available.

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References

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Key words
Breast cancer, Vav1, Akt.