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Know thy cells: commonly used triple-negative human breast cancer cell lines carry mutations in RAS and effectors

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A new article by Tang and coworkers [1] reported that Neuropilin-1 (NRP1) may play a role in tumor stem cell features and the development of claudin-low breast cancer, which, depending on the cell(s)-of-origin and developmental trajectories, could be defined as a molecular subtype or as a phenotype of other intrinsic subtypes [2]. The work further highlights the significance of oncogenic RAS/MAP kinase signaling that has been reported earlier to be a recurrent feature across claudin-low breast tumors [3]. Discussing the potential implications of their work, Tang and colleagues stated that mutations in RAS/MAPK are infrequent in human breast cancers and that NRP1 expression might be the crucial link for the activation of RAS through receptor tyrosine kinases (RTKs). Based on the experimental work presented, such a conclusion should be taken with caution due to the simple fact that three of the four claudin-low tumor cell lines used in this study carry mutations in KRAS (MDA-MB-231) and HRAS (SUM159PT, Hs578T) [4]. Moreover, all three cell lines have mutations in RAS effector pathways. Specifically, MDA-MB-231, which is the most commonly used triple-negative breast cancer cell line model (over 18,000 citations in PubMed), carries mutations in *BRAF* and *NF1* (COSMIC). Oncogenic RAS signaling is an important genetic element for the transformation of primary human cells [5], and it should be noted that many human cancer cell line models that are being employed in breast cancer research carry mutations in the RAS pathway, including MCF10AT (HRAS) and its derivative MCF10DCIS.com (Cellosaurus) as well as most de novo transformed HMECs with RAS^{G12D} from various laboratories such as those of Drs. Weinberg, Band, and Eaves, [6–8]. Beyond the events associated with neoplastic transformation, a high activation of RAS signaling specifically in claudin-low breast cancers seems to be a molecular determinant for the mesenchymal characteristics. Recent work from our team has demonstrated that oncogenic RAS signaling promotes cellular plasticity and the genesis of primary claudin-low mammary tumors in genetically engineered mice [9]. The persistent activation of this pathway seems to be critical for the preservation of the mesenchymal features that define this molecular tumor subtype.

Despite gene expression data from human tumors and experimental evidence using genetic models that support important roles of oncogenic RAS/MAPK signaling in mammary cancer initiation and progression, the importance of this pathway is often diminished by comments about the infrequent occurrence of RAS mutations in primary human breast cancers. It should be noted that breast cancer is not a single disease, and the rates of mutations vary among molecular subtypes and whether the underlying cause of a malignant tumor is hereditary or sporadic. Pathogenic mutations in BRCA1 or BRCA2 are not substantially more common than RAS mutations across all cases, and when it comes to hereditary cancers, patients with certain RASopathies are at greater risk of developing early-onset breast cancer [10]. Studies have shown that genetic alterations in RAS and

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MAP kinases, as well as loss of NF1, occur more often in TNBCs [11]. Additionally, RAS/MAPK pathway alterations were reported to be enriched in residual breast cancers following chemotherapy [12], and it may therefore not be surprising that many established TNBC cell lines that were derived from distant metastases, including those used in the study by Tang et al., have mutations in KRAS or HRAS and their downstream effectors. While these mutations greatly amplify the strength and duration of the signaling pathway, the functionality of mutant RAS may require upstream activators. Hence, the specific upregulation of NRP1 in claudin-low breast cancer and its potential role in RTK signaling in the new report by Tang et al. might be important, but the presence of multiple driver mutations within the pathway of the particular cellular models must be taken into consideration to accurately assess the contribution of NRP1 as a signaling modulator for RAS and MAP kinases and the cellular characteristics that they instigate.

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