R-Ras2 is a transforming GTPase that shares downstream effectors with Ras subfamily proteins. However, little information exists about the function of this protein in tumorigenesis and its signalling overlap with classical Ras GTPases. Here we show, by combining loss- and gain-of-function studies in breast cancer cells, mammary epithelial cells and mouse models, that endogenous R-Ras2 has a role in both primary breast tumorigenesis and the late metastatic steps of cancer cells in the lung parenchyma. R-Ras2 drives tumorigenesis in a phosphatidylinositol-3 kinase (PI3K)-dependent and signalling autonomous manner. By contrast, its prometastatic role requires other priming oncogenic signals and the engagement of several downstream elements. R-Ras2 function is required even in cancer cells exhibiting constitutive activation of classical Ras proteins, indicating that these GTPases are not functionally redundant. Our results also suggest that application of long-term R-Ras2 therapies will result in the development of compensatory mechanisms in breast tumours.

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