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ANNOTATION

year

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PKA signaling drives mammary tumorigenesis through Src.

authors

Beristain AG, Molyneux SD, Joshi PA, Pomroy NC, Di Grappa MA, Chang MC, Kirschner LS, Privé GG, Pujana MA, Khokha R

journal

Oncogene; 2015 Feb 26; 34(9) 1160-73. doi:10.1038/onc.2014.41

abstract

Protein kinase A (PKA) hyperactivation causes hereditary endocrine neoplasias; however, its role in sporadic epithelial cancers is unknown. Here, we show that heightened PKA activity in the mammary epithelium generates tumors. Mammary-restricted biallelic ablation of Prkar1a, which encodes for the critical type-I PKA regulatory subunit, induced spontaneous breast tumors characterized by enhanced type-II PKA activity. Downstream of this, Src phosphorylation occurs at residues serine-17 and tyrosine-416 and mammary cell transformation is driven through a mechanism involving Src signaling. The phenotypic consequences of these alterations consisted of increased cell proliferation and, accordingly, expansion of both luminal and basal epithelial cell populations. In human breast cancer, low PRKAR1A/high SRC expression defines basal-like and HER2 breast tumors associated with poor clinical outcome. Together, the results of this study define a novel molecular mechanism altered in breast carcinogenesis and highlight the potential strategy of inhibiting SRC signaling in treating this cancer subtype in humans.

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ANNOTATION

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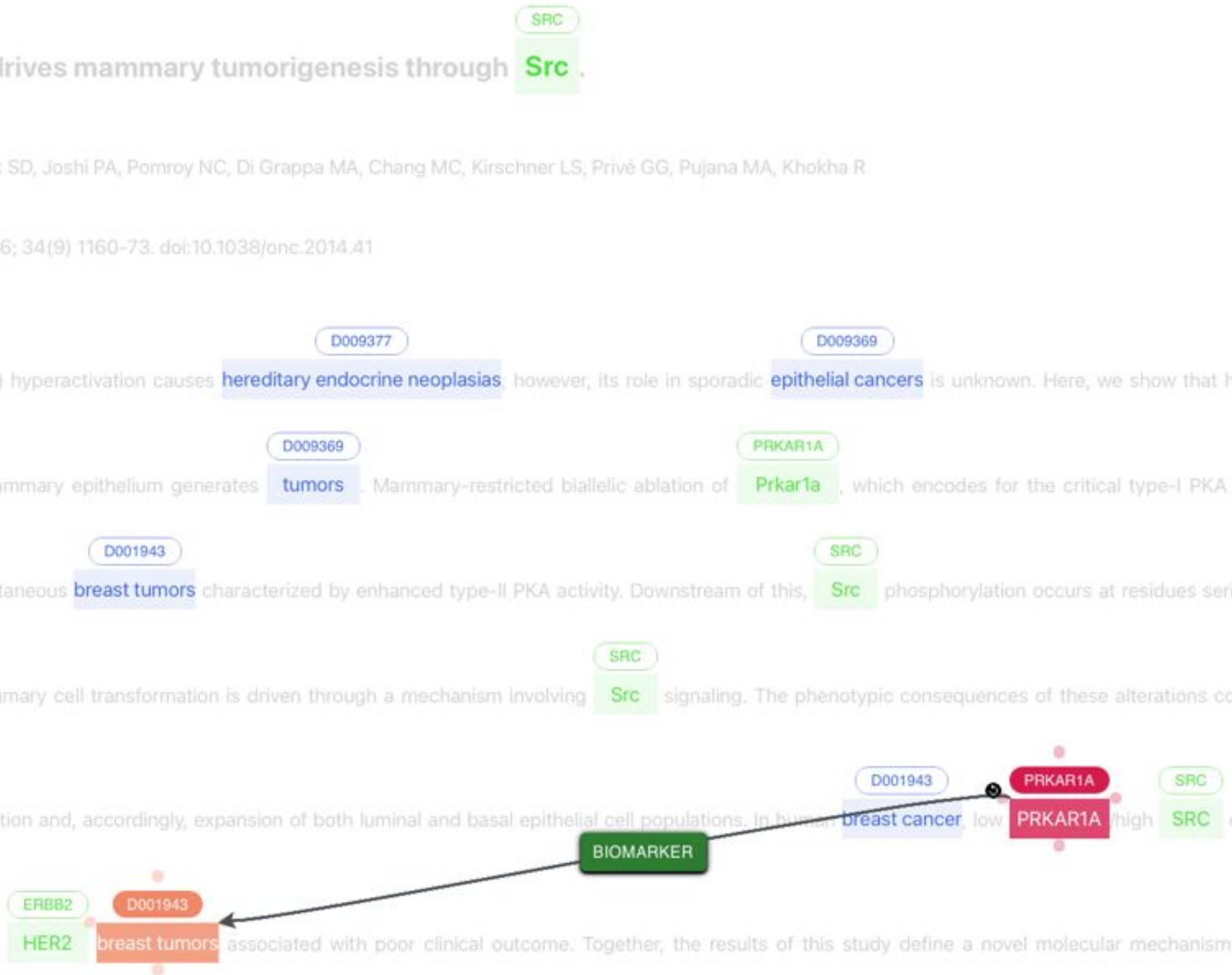
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Relationships

Subject

Gene (6)

PRKAR1A

PRKAR1A

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