2016 LPS GGD Best Paper Award: Nithya Kartha

The Chromatin Remodeling Component *Arid1a* Is a Suppressor of Spontaneous Mammary Tumors in Mice

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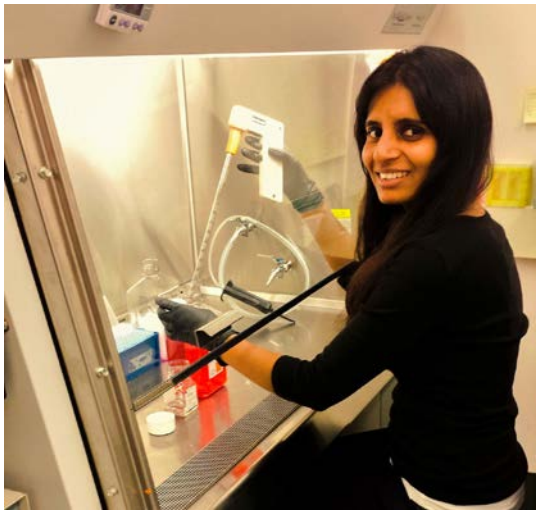
ABSTRACT Human cancer genome studies have identified the SWI/SNF chromatin remodeling complex member *ARID1A* as one of the most frequently altered genes in several tumor types. Its role as an ovarian tumor suppressor has been supported in compound knockout mice. Here, we provide genetic and functional evidence that *Arid1a* is a *bona fide* mammary tumor suppressor, using the Chromosome aberrations occurring spontaneously 3 (*Chaos3*) mouse model of sporadic breast cancer. About 70% of mammary tumors that formed in these mice contained a spontaneous deletion removing all or part of one *Arid1a* allele. Restoration of *Arid1a* expression in a *Chaos3* mammary tumor line with low *Arid1a* levels greatly impaired its ability to form tumors following injection into cleared mammary glands, indicating that ARID1A insufficiency is crucial for maintenance of these *Trp53*-proficient tumors. Transcriptome analysis of tumor cells before and after reintroduction of *Arid1a* expression revealed alterations in growth signaling and cell-cycle checkpoint pathways, in particular the activation of the TRP53 pathway. Consistent with the latter, *Arid1a* reexpression in tumor cells led to increased *p21* (*Cdkn1a*) expression and dramatic accumulation of cells in G2 phase of the cell cycle. These results not only provide *in vivo* evidence for a tumor suppressive and/or maintenance role in breast cancer, but also indicate a potential opportunity for therapeutic intervention in ARID1A-deficient human breast cancer subtypes that retain one intact copy of the gene and also maintain wild-type TRP53 activity.



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