

MULTIPLE FUNCTIONS OF TUMOR SUPPRESSOR BARD1 IN CONTROL OF CELL PROLIFERATION IN DEVELOPMENT AND MALIGNANT TRANSFORMATION

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The BRCA1-associated protein BARD1 was considered as tumor suppressor in conjunction with BRCA1. Work from our group has shown that repression of BARD1 leads to pre-malignant transformation and genomic instability, and that BARD1 is a mediator of apoptosis since i) cell death in vivo and in vitro is accompanied by increased levels of BARD1 protein and mRNA; ii) overexpression of BARD1 induces apoptosis; iii) BARD1-repressed cells are defective for the apoptotic response to genotoxic stress. Since apoptosis is an important mechanism in tissue developmental and homeostasis and in suppression of tumorigenesis, we analyzed BARD1 expression in various healthy and malignant tissues.

The protein sequence required for apoptosis induction could be delimited to a region that harbors two tumor-associated missense mutations of BARD1, thus confirming BARD1's role in tumor suppression through signaling from proapoptotic stress towards induction of apoptosis. The apoptotic function of BARD1 is amplified in spermatogenesis by the expression of a differentially spliced isoform of BARD1 comprising the apoptotic region but lacking the BRCA1 interacting RING finger thus resulting in increased apoptotic activity. Increased BARD1 expression is observed in tissues with rapid cellular turn over (e.g. testis, spleen, colon). Interestingly however, in tumor tissues its expression is variable, reflecting multiple patterns of loss of function and gain of function.