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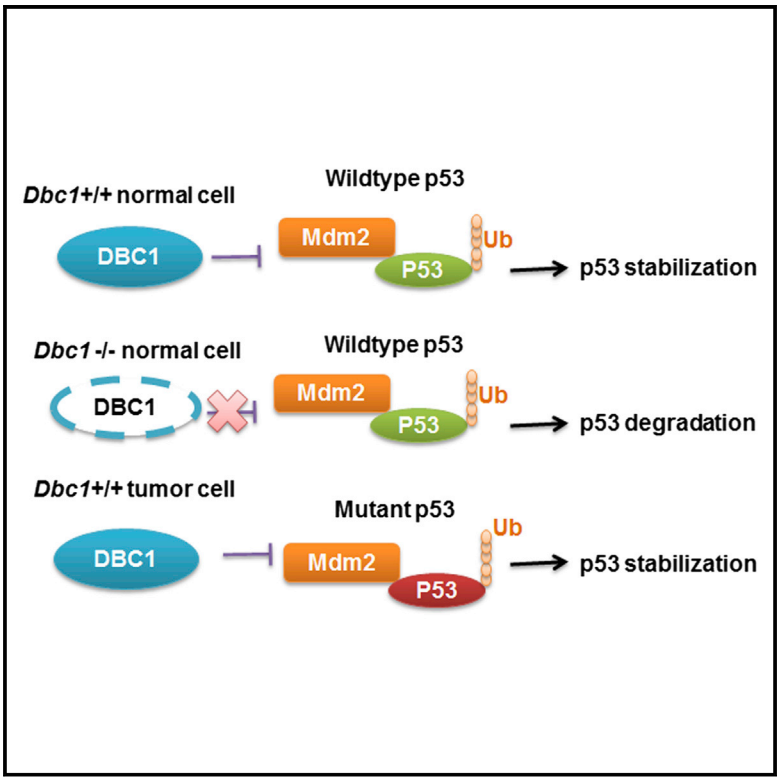
DBC1 Functions as a Tumor Suppressor by Regulating p53 Stability

Graphical Abstract



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In Brief

Qin et al. now find that DBC1 loss results in reduced p53 protein. DBC1 directly binds p53 and stabilizes it through competition with MDM2, indicating that DBC1 plays an important role in tumor suppression through p53 regulation.

Highlights

- DBC1 is a tumor suppressor
- Loss of DBC1 promotes tumorigenesis in a p53-dependent and SIRT1-independent manner
- DBC1 stabilizes p53 through competition with Mdm2
- DBC1 also stabilizes mutant p53

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DBC1 Functions as a Tumor Suppressor by Regulating p53 Stability

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SUMMARY

DBC1 (deleted in breast cancer 1), also known as CCAR2 or KIAA1967, is an important negative regulator of SIRT1 and cellular stress response. Although the *Dbc1* gene localizes at a region that is homozygously deleted in breast cancer, its role in tumorigenesis remains unclear. It has been suggested to be either a tumor suppressor or an oncogene. Therefore, the function of DBC1 in cancer needs to be further explored. Here, we report that *Dbc1* knockout mice are tumor prone, suggesting that DBC1 functions as a tumor suppressor in vivo. Our data suggest that the increased tumor incidence in *Dbc1* knockout mice is independent of *Sirt1*. Instead, we found that DBC1 loss results in less p53 protein in vitro and in vivo. DBC1 directly binds p53 and stabilizes it through competition with MDM2. These studies reveal that DBC1 plays an important role in tumor suppression through p53 regulation.

INTRODUCTION

p53 is a pivotal tumor suppressor and one of the most mutated genes in human cancer, with p53 mutations observed in over half of all human cancers (Brady and Attardi, 2010; Vousden and Prives, 2009). p53 regulates multiple cellular functions, including apoptosis, cell cycle arrest, cell metabolism, and senescence. One of the major regulatory mechanisms of p53 is its ubiquitination by a ubiquitin E3 ligase MDM2 (murine double minute 2), which leads to p53 degradation under normal conditions (Haupt et al., 1997). Under stress conditions, such as DNA damage, viral infection, and oncogene activation, p53 is quickly accumulated, resulting in its activation. Several mechanisms are responsible for p53 induction, including MDM2 inactivation, interrupted interaction between p53 and MDM2, and activation of ubiquitin proteases (Dai and Gu, 2010).

The *Dbc1* gene was initially discovered as a gene deleted in human chromosome 8p21 in breast cancer (Hamaguchi et al., 2002). DBC1 is composed of a leucine zipper motif at the amino terminus, coiled coil domain at the carboxy terminus, a nuclear localization signal, an EF hand domain, and a Nudix domain (Anantharaman and Aravind, 2008; Kim et al., 2008). DBC1 is processed into C-terminal p120 and p66 fragments, which relocate from nucleus to mitochondria and enhance apoptotic signaling with tumor necrosis factor-α (TNFα) treatment in HeLa cells (Sundararajan et al., 2005). Several studies also suggest that DBC1 regulates hormone receptor activity. For instance, DBC1 activates retinoic acid receptor α and androgen receptor and represses transcription activity of estrogen receptor β (Fu et al., 2009; Garapaty et al., 2009; Koyama et al., 2010). Furthermore, we and others have found that DBC1 negatively regulates SIRT1 activity through binding to its active site (Kim et al., 2008; Zhao et al., 2008). DNA damage and oxidative stress increase the DBC1-SIRT1 interaction, whereas PKA and AMPK induce dissociation of SIRT1 from DBC1 (Yuan et al., 2012; Nin et al., 2012). DBC1 also binds to methyltransferase SUV39H1 and inhibits cellular H3K9 methylation (Li et al., 2009).

The role of DBC1 in tumorigenesis is more puzzling. *Dbc1* is deleted in several types of cancer and has been suggested to suppress tumor development (Hamaguchi et al., 2002; Kim et al., 2009; Di Marcotullio et al., 2011). DBC1 is also associated with good outcome in gastric cancer (Noguchi et al., 2014), but other studies have shown that DBC1 is overexpressed in breast cancer, gastric cancer, and other tumor types and is correlated with poor prognosis (Cha et al., 2009; Hiraike et al., 2010; Kang et al., 2012; Zhang et al., 2014). Downregulation of DBC1 inhibits the proliferation and invasive potential of gastric cancer cells (Bae et al., 2014). Because of these conflicting findings, DBC1 function in tumorigenesis remains unclear.

Here we show that p53 level is decreased in DBC1-deficient cells and tissues. DBC1 binds to the N terminus and DNA binding domain of p53, competing with MDM2 and stabilizing p53. Depletion of *Dbc1* promotes tumorigenesis in mice.

RESULTS

DBC1 Loss Promotes Tumorigenesis

To test that DBC1 is a bona fide tumor suppressor in vivo, we generated *Dbc1* knockout (KO) mice. $Dbc1^{+/+}$, $Dbc1^{+/-}$, and $Dbc1^{-/-}$ mice were monitored for 24 months. *Dbc1* KO mice were born in expected Mendelian ratios (Table S1), but