Abstract  More than a decade ago, the *BRCA1* and *BRCA2* genes, responsible for familial breast cancers, were discovered. About 50 percent of women diagnosed with breast cancer have inherited mutations in BRCA1 or BRCA2 that predispose them to breast and ovarian cancer. Although there are several thousand publications concerning analysis of structure, expression, and function of these genes, no treatment methods for breast cancer have been developed that based on the accumulated knowledge. BRCA1 and BRCA2 are large proteins that interact with many other proteins of diverse functions. One particular protein, BARD1, a binding partner of BRCA1, might crucially regulate the tumor suppressor function of BRCA1 and act as a tumor suppressor in its own right. The functions attributed to BARD1 might make it indispensable for cell viability. This might explain why BARD1 mutations are rarely found in cancer, but aberrant truncated forms are overexpressed. Disappointingly, while screening for mutations in the predisposition genes BRCA1 and BRCA2 is now routinely carried out, no treatment methods have been developed that are based on our knowledge of BRCA1 and BRCA2 functions, which leaves mutation carriers without hope for future treatment. It will be interesting how dissection of the functions of BARD1 will open new avenues for cancer treatment. Here we discuss that BARD1 expression can be regulated in a cell cycle dependent way, in a hormone dependent was, and by hypoxia and oxidative stress. Understanding the way how BARD1 is activated will be important the understanding of its role in tumorigenesis and in the search for treatment targets.

Keywords  BARD1, BRCA1, BRCA2, breast cancer, ovarian cancer, apoptosis, cancer therapy

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Introduction

The BRCA1-associated RING domain 1 (BARD1) was discovered in a yeast two-hybrid screen as a binding partner of BRCA1 (Wu et al., 1996). BARD1 and BRCA1 have several features in common, namely, similar protein structure, embryonic lethality of knockouts in mouse models (McCarthy et al., 2003), and induction of genetic instability when depleted from cells (Irminger-Finger et al., 1998; Joukov et al., 2001; McCarthy et al., 2003). The prevalent opinion in the field is that BARD1 only acts as an accessory protein for BRCA1. However, several reports have demonstrated the BRCA1-independent functions of BARD1, primarily in apoptosis (Fig. 15.1). Additionally, data have accumulated in the last three years that suggest a role of BARD1, as well as BRCA1 and BRCA2, in mitosis, which might link their functions and explain their role in maintaining genetic stability. The expression of BARD1 is upregulated in most proliferating tissues and it is low in quiescent cells. This is consistent with the activation of BARD1 transcription by the transcription factor E2F (Ren et al., 2002). The diverse functions of BARD1, in regulation of cell proliferation and apoptosis and its role as tumor suppressor in normal cells and as oncogene when expressed as truncated isoform in tumors, suggest that it is of importance to understand the regulators of BARD1 expression, such as hypoxia, and hormones.

BARD1: A Stress-Response Factor?

The function of BARD1 as inducer of apoptosis was discovered in cells treated with doxorubicin, a chemotherapeutic drug. Doxorubicin induces DNA damage, therefore BARD1 transcriptional activation was thought to be induced by a DNA damage pathway (Irminger-Finger et al., 2001). However, doxorubicin also generates

Fig. 15.1 The BARD1 protein. (A) BARD1 domain structure compared to BRCA1. RING (green), ANK (blue), and BRCT (red) domains are indicated and location of potential NLS (light blue). Evolutionary conservation is indicated as percentage of identical amino acids between mouse and human sequence within distinct regions.