Women harboring mutations in the tumor suppressor gene BRCA1 (breast cancer 1, early onset) have a profound predisposition to early-onset breast or ovarian cancer or both. BRCA1-associated breast tumors are characteristically 'basal-like', containing minimal estrogen receptor (ER), progesterone receptor (PR), and HER2 and expressing 'basal' cytokeratins and epidermal growth factor receptor. Basal-like tumors were originally defined on the basis of microarray studies, in which their molecular signature suggested similarities to basal cells resident in normal breast epithelium. Such observations led to the hypothesis that BRCA1-associated tumors arose from stem cells. Moreover, mammary stem cells exhibit a similar 'triple-negative' phenotype. BRCA1 plays a crucial role in orchestrating the response to double-stranded DNA damage but is recognized to have multiple other functions. In vitro cellular assays have indicated roles in regulating mammary epithelial cell proliferation and differentiation and in promoting luminal-to-basal lineage transdifferentiation [1-4]. The ability to fractionate mammary epithelium into different subtypes has enabled insights into target cells prone to tumorigenesis. Using human breast tissue, Liu et al. [5] observed that BRCA1 was required for ER-negative stem/progenitor cells to differentiate into mature ER-positive luminal cells. Lim et al. [6] evaluated pathologically normal primary breast tissue samples from haploinsufficient BRCA1 patients and identified an aberrant luminal progenitor population with factor-independent growth properties. A similar observation was made in Brca1-deficient mice [6]. Consistent with a luminal progenitor cell defect, breast tissue from BRCA1 mutation carriers generally showed an increase in this subset relative to the total epithelial population. Moreover, the molecular signature of luminal progenitor cells was found to be more similar to that of basal-like tumors than to that of any other tumor subtype [6]. Overall, these findings indicated, but did not prove, that luminal progenitors are the 'cells-of-origin' for basal-like tumors arising in BRCA1 carriers. An important study by Molyneux et al. [7] conditionally deleted Brca1 in different epithelial populations (heterozygous for p53) and revealed that luminal rather than basal cells were predisposed to basal-like mammary tumors. These in vivo experiments provided direct evidence that BRCA1-associated breast cancers can arise from luminal ER-negative progenitors.

A recent study by Proia et al. [8] further highlighted the relevance of luminal cells in haploinsufficient BRCA1 human breast tissue. With an elegant in vivo assay, fresh breast epithelial cells from wild-type or BRCA1<sup>-/mutat</sup> women were simultaneously transduced with potent lentiviruses encoding mutant p53, cyclin D1, activated phosphoinositide 3-kinase (PI3K), and oncogenic K-ras and implanted into humanized mammary fat pads of nonobese diabetic/severe combined immunodeficiency disease (NOD/SCID) mice. Whereas luminal and basal-like tumors arose in mice implanted with wild-type cells, BRCA1<sup>-/mutat</sup> cells largely yielded basal-like tumors.
indicative of a preprogrammed epithelial defect that dictates tumor phenotype. Proia et al. [8] also used epithelial subsets to demonstrate preferential transformation of luminal compared to basal cells.

Gene profiling of wild-type and BRCA1+/mut breast epithelia generated a molecular signature enriched for Wnt, Notch, and melanogenesis signaling pathways in BRCA1+/mut tissue. Those findings prompted an evaluation of the transcriptional repressor SLUG, which can be activated by these pathways. SLUG is a member of the SNAIL family and has been shown to have an important role in coordinating the epithelial-mesenchymal transition and programming cells toward a basal-like phenotype in breast cancer [9-11]. SLUG is normally expressed in the basal/stem cell-enriched population in both mice and humans [12]. Interestingly, although SLUG mRNA levels were unperturbed in BRCA1+/mut tissue, abundant levels of SLUG protein were observed. Moreover, knockdown of BRCA1 by short interfering RNAs in breast cell lines resulted in a twofold increase in SLUG protein. Conversely, knockdown of SLUG in breast epithelial cells biased them toward a more luminal cell fate [8]. Thus, BRCA1 appears to regulate SLUG protein stability, and this may directly influence the cell fate specification of luminal progenitor cells. The precise mechanism through which BRCA1 contributes to SLUG protein stabilization remains to be elucidated. A direct interaction between SLUG and BRCA1 was not found, nor did knockdown of the BRCA1-associated RING domain-1 protein (BARD1) alter SLUG levels [8]. The interesting link between BRCA1 and SLUG in perturbing cell fate decisions will undoubtedly form the basis of future studies.

Despite similarities in the epithelial subsets defined by EpCAM and CD49f by Proia et al. [8], there are also some noteworthy differences. In contrast to previous authors [6,13,14], Proia et al. [8] describe two potentially distinct basal subsets: an EpCAMlow population (‘basal/myoepithelial’) and an EpCAM+ population (‘mesenchymal’ or ‘basal progenitor’) [15], the latter of which appears to be novel. This subset was found to be expanded in BRCA1+/mut breast tissue (with no change in the luminal progenitor subset) and was attributed to diversion of luminal cells toward a basal cell fate. On the other hand, we observed a significant decrease in the basal subset [6] as well as reduced numbers of mammary stem cells in mice. In addition, the mature luminal subpopulation contained a dramatically increased number of CK5/6-expressing cells and fewer PR-positive cells, consistent with a perturbation in differentiation [6]. These differing observations may, in part, reflect different methodological approaches (magnetic beads versus flow cytometry for lineage depletion) and gating strategies used for cell fractionation as well as possible variation between breast samples. Of the 12 BRCA1+/mut samples described by Proia et al. [8], at least a third of patients had prior breast cancer. Chemotherapy or endocrine therapy may modify epithelial cell composition. Regardless of these differences, both studies identify BRCA1 as a key regulator of luminal cells.

In summary, one striking consequence of BRCA1 deficiency in mammary epithelium appears to be perturbed cell fate specification, in which luminal cells are biased toward a more basal-like phenotype [8]. Luminal progenitor cells presumably depend, in part, on BRCA1 for providing high-fidelity DNA repair, as they are highly proliferative. Altered proliferative and differentiative properties, compounded by a predisposition to genomic instability, are likely to set the stage for neoplastic transformation. It seems likely that somatic gene silencing of BRCA1 through epigenetic mechanisms plays a similarly important role in sporadic basal-like breast cancer. Further elucidation of molecular perturbations resulting from BRCA1 deficiency will hopefully provide important clues on therapeutic targets relevant to breast cancer treatment and chemoprevention for high-risk women.

Abbreviations
BRCA1, breast cancer 1, early onset; ER, estrogen receptor; PR, progesterone receptor.

Competing interests
The authors declare that they have no competing interests.

Author details
1Stem Cells and Cancer Division, The Walter and Eliza Hall Institute of Medical Research, 1G Royal Parade, Parkville, VIC 3052, Australia. 2Familial Cancer Centre, The Royal Melbourne Hospital, Grattan Street, Parkville, VIC 3050, Australia. 3Department of Medicine, The University of Melbourne, Parkville, VIC, 3010, Australia; 4Department of Medical Biology, The University of Melbourne, Parkville, VIC 3010, Australia.

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