News Release

Title

BRCA1 haploinsufficiency impairs iron metabolism to promote chrysotile-induced mesothelioma via ferroptosis-resistance

Key Points

- *Brca1* mutant rats were more likely to develop high-grade mesothelioma.
- BRCA1 haploinsufficiency promoted chromosomal deletion, especially *Cdkn2a/2b,* in chrysotile-induced mesothelioma.
- BRCA1 haploinsufficiency impaired iron metabolism.
- BRCA1 haploinsufficiency promoted ferroptosis-resistance after asbestos exposure.

Summary

Malignant mesothelioma (MM) is still a social burden associated with asbestos exposure. Local iron accumulation thereby represents the major pathogenesis, followed by oxidative DNA strand breaks and genomic alterations in the mesothelium. BRCA1 is a critical component of homologous recombination repair directed to DNA double-strand breaks. Whereas *BRCA1* germline mutation is an established risk for breast/ovarian cancer, its role in MM development remains to be elucidated. Murine Brca1 mutant models thus far have not reproduced human phenotypes. However, a rat *Brca1* mutant model (Mut; L63X/+) recently reproduced them at least partially. Here we describe the differential induction of MM in *Brca1* mutant rats by intraperitoneal injection of chrysotile or crocidolite. Only Mut males injected with chrysotile revealed a promotional effect on mesothelial carcinogenesis in comparison to *wild-type* and/or females, with all the MMs *Brca1*-haploinsufficient. Array-based comparative genomic hybridization of MMs disclosed a greater extent of chromosomal deletions in *Brca1* mutants, including *Cdkn2a/2b* accompanied by *Tfr2* amplification, in comparison to *wild-type* tumors. Mutant MMs indicated iron metabolism dysregulation, such as increase in catalytic Fe(II) and Ki67-index as well as decrease in Fe(III) and ferritin expression. Simultaneously, mutant MMs revealed ferroptosis-resistance by upregulation of Slc7A11 and Gpx4. At an early carcinogenic stage of 4 weeks, induced Brca1 expression in mesothelial cells was significantly

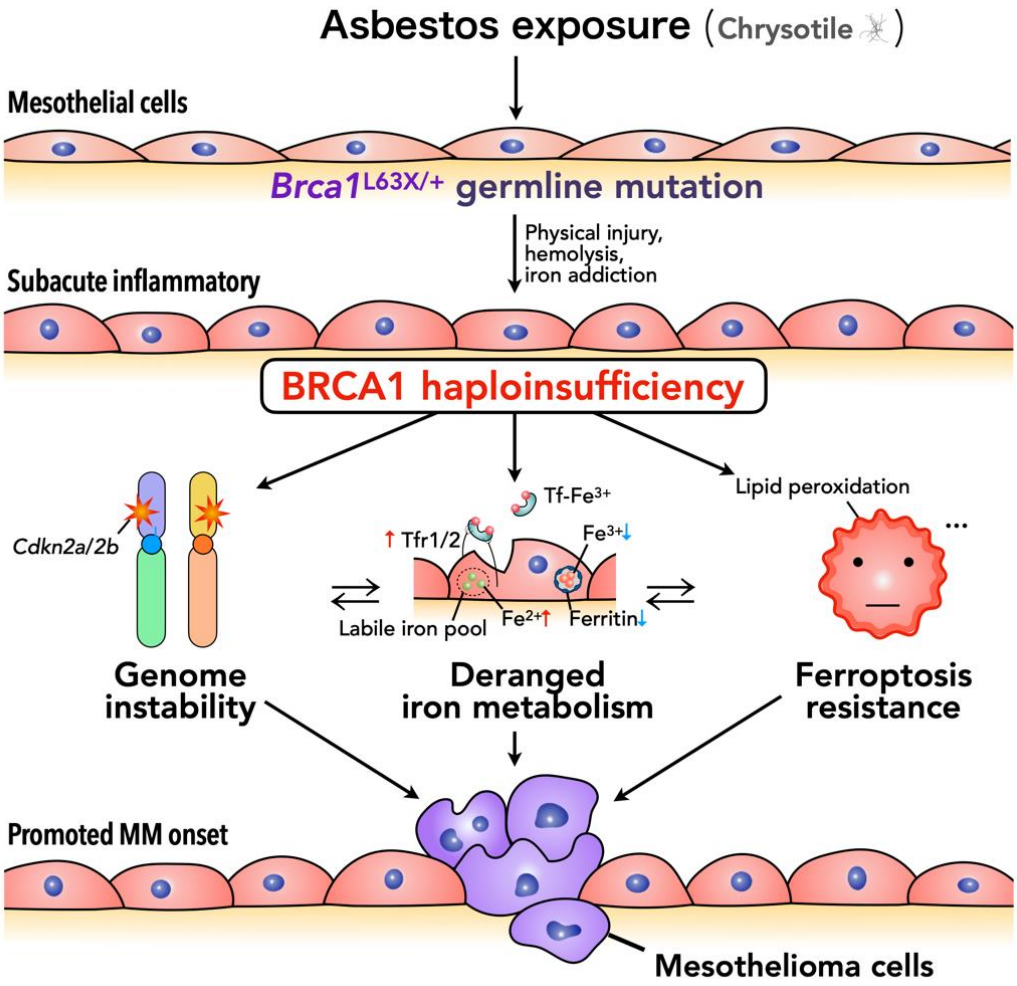
suppressed in chrysotile/Mut in comparison to crocidolite/Mut whereas significant preference to iron with decrease in Fe(III) has been already established. In conclusion, chrysotile exposure can be a higher risk for MM in BRCA1 mutant males, considering the rat results.

Research Background

Asbestos exposure is a social problem due to its risk of malignant mesothelioma, in which excess iron plays an important role in carcinogenesis. As a tumor suppressor, BRCA1 mainly functions by maintaining DNA integrity and has gained increasing attention for its role in predicting tumorigenesis and its treatment. However, the association of BRCA1 to MM carcinogenesis is still unelucidated whereas studies on familial MM syndrome have identified BAP1 (BRCA1-associated protein-1) as responsible . Here we for the first time undertook to evaluate the significance of BRCA1 in MM carcinogenesis.

Research Results

To investigate the role of BRCA1 in asbestos-induced mesotheliomagenesis, we compared *Brca1*$^{L63X/+}$ (Mutant) rats with *wild-type* ones by using an asbestos-induced mesothelioma model. As compared with *wild-type* group MMs, the *Brca1* mutant group MMs revealed a higher Ki67-index with a greater proportion of sarcomatoid histotypes. Immunohistochemical analysis showed that BRCA1 expression was proportionally associated with survival and inversely associated with nuclear grade. Ferroptosis-related proteins such as GPX4 and SLC7A11(xCT) were significantly reduced in *Brca1* mutant rats a few weeks after chrysotile exposure, implying that ferroptosis resistance occurred, which may contribute to earlier onset of mesothelioma.



This suggests that BRCA1 deficiency leads to ferroptosis-resistance earlier in mesothelial cells and thus facilitates tumorigenesis.

Future Perspective

Chrysotile exposure can be a higher but avoidable risk for MM in BRCA1 mutant males than the general population. This male preponderance is the same for humans, and further investigation are needed from the viewpoint of sex hormones.

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