

Gene x environment interactions may help reduce mesothelioma risk

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Researchers have recently discovered that certain enzymes bind to each other may help lessen the risk of developing mesothelioma, a cancer of the lining of the lungs and abdomen. The study from University of Hawai'i Cancer Center's Flavia Novelli, Michele Carbone and Haining Yang was published in the *Proceedings of the National Academy of Sciences* of the U.S. They reported that the interaction of

BAP1 (a tumor suppressor gene), HMGB1 (nuclear protein) and HDAC1 (histone deacetylase) form a trimer, a macromolecular component made up of multiple molecules, which may improve mesothelioma outcomes.

For many years, researchers at the UH Cancer Center have been at the forefront of [mesothelioma](#) research. Carbone and Yang discovered that mutations of the gene called BAP1 cause mesothelioma and other cancers. BAP1 is a powerful [tumor suppressor gene](#), which means that when this gene is inactivated by mutations, the risk of developing [cancer](#) significantly increases. In [parallel studies](#), Carbone and Yang discovered that asbestos causes the extracellular release of HMGB1, a protein that promotes inflammation and mesothelioma.

Novelli's discovery brings Carbone and Yang's research together. She found that when the levels of BAP1 are reduced due to mutations, the BAP1-HMGB1-HDAC1 trimer is disrupted and HMGB1, a nuclear protein, is released extracellularly, triggering cancer. This process is enhanced by exposure to asbestos, which also causes the release of HMGB1. Therefore, carriers of BAP1 mutations are very susceptible to asbestos carcinogenesis and mesothelioma.

"Our findings explain mechanistically the observed gene ^x environment interaction in mesothelioma that occurs in carriers of germline BAP1 mutations exposed to asbestos," said Novelli, a postdoctoral researcher and first author of the paper. "This publication is the result of amazing teamwork and collaboration between many incredible international scientists. The outcome is a meaningful research paper that we hope will help prevent cancer and improve many people's lives."

Encouragingly, Novelli and collaborators found that reducing HMGB1 activity with aspirin or other chemicals in mice that carry BAP1 [mutations](#) and are exposed to asbestos significantly reduced the number

of mice that developed mesothelioma.

Going forward, the researchers, in collaboration with Marcus Tius, professor of chemistry at UH Mānoa, will search the Native Hawaiian natural products library to identify and synthesize [small molecules](#) that bind and block the activity of extracellular HMGB1 for clinical trials to prevent or decrease mesothelioma growth.

More information: Flavia Novelli et al, BAP1 forms a trimer with HMGB1 and HDAC1 that modulates gene × environment interaction with asbestos, *Proceedings of the National Academy of Sciences* (2021). [DOI: 10.1073/pnas.2111946118](https://doi.org/10.1073/pnas.2111946118)

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