

Mouse Model For Mesothelioma Reproduces Human Disease

ScienceDaily (Mar. 11, 2008) — Scientists have established a mouse model for human malignant mesothelioma that will provide valuable insight into cancer development and progression along with new directions for design of therapeutic strategies. The research, published by Cell Press in the March issue of *Cancer Cell*, may eventually lead to a substantially improved outlook for patients with this devastating disease.

Malignant mesothelioma is an aggressive cancer originating from the mesothelial lining of the pleural cavity. Malignant mesothelioma is associated with asbestos exposure and is characterized by a long latency period between exposure and disease onset. Chemotherapy can sometimes lead to improvement of overall survival but there is no cure for malignant mesothelioma and patients often succumb from the disease within a year of diagnosis. "There is an urgent need for experimental models of malignant mesothelioma that can be used to not only study the onset and progression of the disease, but also to serve as a model to select new combination therapies and targeted agents," says study leader, Dr. Anton Berns, from The Netherlands Cancer Institute.

In humans, malignant mesothelioma has been associated with genetic lesions that result in the loss of Neurofibromatosis type 2 (NF2) and genetic lesions affecting RB and P53 pathways. Dr. Berns' team investigated whether a range of conditional single or compound mutations in the Nf2, p53 and Rb pathways within the mesothelial lining of the thoracic cavity would cause malignant mesothelioma in mice.

The researchers found that the vast majority of mice with conditional Nf2;Ink4a/Arf and Nf2;p53 mutations developed MM after a short latency period. The mouse malignant mesothelioma tumors, which could be followed noninvasively through the use of bioluminescence imaging, closely resembled human MM. Interestingly, Nf2;Ink4a/Arf knockout mice had a more invasive cancer when compared with Nf2;p53 knockout mice. The researchers went on to show that the loss of Ink4a makes a substantial contribution to the poor clinical outcome of murine malignant mesothelioma .

These results describe an excellent model system for investigating the molecular mechanisms that underlie malignant mesothelioma . "Our mouse models should be suitable to further dissect pathways critically important in mesothelioma development and progression and serve as invaluable tools to test new intervention strategies," concludes Dr. Berns. "We have also derived a series of cell lines that reproduce the disease when grafted into the thoracic cavity. These may also facilitate design of better MM therapies."

The researchers include Johan Jongsma, Erwin van Montfort, Marc Vooijs, John Zevenhoven, Paul Krimpenfort, Martin van der Valk, Marc van de Vijver, and Anton Berns, of The Netherlands Cancer Institute, Amsterdam, The Netherlands.

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