



SCIENCE FOR THE BENEFIT OF HUMANITY

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Novel Mode of Treating Squamous Cell Carcinomas with Nuclear Export Inhibitors

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Technology Summary

Squamous cell carcinomas of the head and neck (HNSCCs) are the sixth most common human cancer worldwide and are caused by a myriad of genetic and epigenetic alterations. HNSCCs are subject to frequent and aggressive recurrences, indicating that current modes of treatment have limited efficacy.

Our investigators have conducted an in vivo RNAi screen in mice to look for alterations in candidate genes that would result in a predisposition to HNSCCs. This screen surprisingly revealed that the gene MYH9, which codes for non-muscular myosin heavy chain IIa, to be a tumor suppressor. It appears that myosin IIa is needed to retain p53 in the nucleus, and lack of nuclear accumulation of p53 as well as myosin IIa deficiency/mutation is strongly associated with various cancers. Therefore, inhibiting nuclear export would stabilize nuclear p53, resulting in a non-cancerous state. In turn, those inhibitors would be a novel way to treat cancers involving MYH9 defects. Our scientists tested the effect of leptomycin B, a well-known nuclear export inhibitor, on cells from Myh9-deficient mice and found improved retention of p53 in the nucleus. In addition to MYH9 mutations, they also found in their analyses of human HNSCCs that a significant percentage of HNSCCs are associated with an absence or reduction of myosin IIa, and that Myh9 deficiencies correlated with shortened survival. Overall, this work shows the utility of a well-designed RNAi screen combined with mouse models and a new relationship between myosin IIa and p53 regulation in cancer. There are also plans to continue the research by studying other nuclear export inhibitors.

Area of Application

Treatment of various cancers caused by defects in MYH9, including head and neck squamous cell carcinoma and epithelial cancers.

Stage of Development

Discovery, in vivo screen in mice, experiments in human keratinocytes from HSNCC samples.

Lead Inventor

Dr. Elaine Fuchs

Patent Information

U.S. patent application US 2015-0148411 pending

References

Schramek, et al. 2014. In vivo RNAi screen unveils myosin IIa as a tumor suppressor of squamous cell carcinomas. *Science*, 343(6168):309-313

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