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Novel targeted treatments for metastatic uveal melanoma

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Metastatic uveal melanoma (mUM) currently has no treatment offering extended survival except for the select patients whose isolated liver metastases can be resected. As a solid tumor, UMforms hypoxic areas which are resistant to treatment since blood-born treatments cannot reach them, and there is not enough oxygen to form destructive free radicals in response to ionizing radiation. Replication competent retroviral (RCR) vectors can deliver shRNAs to target the tumor's defense mechanism against hypoxia while spreading from one cell to the next. We based our RCRs on MuLV, which can only infect replicating cells, creating a double targeting system affecting only hypoxic replicating cells. In order to target the tumor's response to hypoxia we created RCRs delivering shRNA against the regulators of hypoxia: HIF1, HIF2, CREB, and all three together from a polycistronic RNA. We tested the different cell lines and found that not all cell lines have the same sensitivity to hypoxia. Mel270, created from a primary tumor that metastasized, showed a higher resistance to hypoxia than 92.1. After infection the cells stably with the various viruses we could see under hypoxic conditions the additive effect of the various viruses (mostly CREB) in diminishing proliferation and increasing activated caspase 3 levels. Animal studies by subcutaneous and in our direct intrahepatic injection models are underway along with combination treatments to affect also the normoxic area. Taken together, this combined treatment algorithm shows promise in treating mUM.

Biography

Shahar Frenkel has completed his dual MD/Ph.D.degree at the age of 26 years from the Hebrew University of Jerusalem and Postdoctoral studies in University of Illinois at Chicago, and Hadassah-Hebrew University Medical Center. He is an Ocular Oncologist and Ophthalmic Pathologist, and heads a research group aimed at finding novel therapies for uveal melanoma. He has served on the managing board of the International Society of Ocular Oncology. He has published more than 35 papers in reputed journals and has been has been reviewing manuscripts for a number of leading ophthalmic journals.

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