Pierre Hardy, Rui Wang

Houda Tahiri/University of Montreal/Departments of Pediatric, Pharmacology & Physiology, Research Center of CHU Ste-Justine/Montreal/Quebec/Canada

miRNA-driven downregulation of cholesterol biosynthesis through SREBP2 inhibition suppresses uveal melanoma metastasis

Uveal melanoma (UM) is the most common primary intraocular malignant tumor in adults, and metastatic dissemination remains the predominant cause of mortality. Despite advances in cancer therapeutics, effective treatments for metastatic UM remain scarce, underscoring the need to identify novel biological drivers and therapeutic targets. Emerging studies suggest a link between cholesterol metabolism and tumor progression, yet the functional relevance of cholesterol regulation in UM metastasis has not been fully elucidated. We investigated the role of miRNA in regulating UM metastatic behavior using multiple UM cell lines and a suprachoroidal injection mouse model. Functional assays demonstrated that miRNA markedly suppresses cell migration, invasion, and cancer stem-like cell (CSC) formation. Mechanistic analyses revealed that miRNA directly targets sterol regulatory element-binding protein 2 (SREBP2), a key transcriptional regulator of cholesterol biosynthesis. Downregulation of SREBP2 by miRNA resulted in significantly reduced intracellular cholesterol levels. This metabolic shift impaired epithelial-to-mesenchymal transition (EMT) and decreased the CSC population, thereby attenuating metastatic potential. Importantly, restoration of cholesterol levels or forced expression of SREBP2 effectively reversed the anti-metastatic effects of miRNA, confirming the essential role of the miRNA –SREBP2–cholesterol axis. Collectively, our findings identify miRNA as critical regulator of cholesterol metabolism in UM and highlight its potential as a therapeutic strategy for metastatic UM.

Keywords: uveal melanoma, metastasis, cholesterol, SREBP2, lipid metabolism

Biography

Dr. Hardy is a professor and researcher in pediatrics (neonatal), pharmacology, and physiology at the University of Montreal, Canada. He directs the Translational Medicine Research Laboratory at the Sainte-Justine University Hospital Research Centre. He earned a PhD in pharmacology and physiology from the University of Montreal and completed postdoctoral studies at the Institute of Medicine and Engineering at the University of Pennsylvania, USA. His main research areas focus on translational research aimed at developing new anti-angiogenic and antitumor treatments and understanding their mechanisms of action. He is the author of over 150 peer-reviewed publications, book chapters and holds several patents.

doi.org/10.51219/URForum.2026.Pierre-Hardy

ISBN: 978-1-917892-46-9