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Ultraviolet A (UVA) and G alfa q/11-mediated signal transduction in uveal melanoma

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Uveal melanoma (UM) results from the transformation of melanocytes in the uveal tract of the eye and is the most common intraocular malignancy in adults, with >50% chance of forming highly aggressive metastases for which no effective treatment exists. Unlike cutaneous melanoma, UM harbors somatic, mutually exclusive mutations in Guanine nucleotide-binding protein G(q) subunit a (GNAQ) and its paralogue GNA11, which encode closely related members of the Gaq/11 family of G proteins that operate downstream of G protein-coupled receptors (GPCRs) to activate Phospholipase Cb4 (PLCb4), leading to an increase in intracellular Ca2+. Approximately 95% of GNAQ and GNA11 mutations in UM encode the Q209L mutation that results in constitutive activity of the GTP-ase and melanocyte transformation. Recent data revealed additional mutations in PLCb4 and Cysteinyl leukotriene receptor 2 (CYSLTR2) mutually exclusive with Gaq/11 mutations, suggesting that UM is defined by activating mutations in the Gaq/11 pathway1. Uncovering the mechanisms involved in UM requires a thorough investigation of Gaq/11 signaling in uveal melanocytes and understanding whether the activating mutations are necessary and sufficient for UM development. The Oancea lab has recently discovered in human epidermal melanocytes a Gaq/11-mediated pathway activated by physiological doses of UVA2a protective response mediated by epidermal melanocytes, chronic exposure can lead to skin cancer and photoaging. However, the molecular mechanisms that allow human skin to detect and respond to UVR remain incompletely understood. UVR stimulates a retinal-dependent signaling cascade in human melanocytes that requires GTP hydrolysis and phospholipase C \u03b2 (PLC\u03b2. Our preliminary results show that this pathway is conserved in 4 different UM cell lines and reveal significant differences between the UM cells that harbor the Q209L mutation compared to the ones that express the wild type Gaq/11. To understand the function of Gaq/11 in non-transformed cells, we extracted and cultured primary uveal melanocytes from the choroid, ciliary body and iris of cow eyes. In addition, the RNAseq data analysis performed on 80 UM patients highlighted that several G-proteins and GPCRs are highly expressed suggesting a possible correlation with the tumor genesis. Our goal is to develop a functional uveal melanocyte culture based on cow eyes and to compare UVA and other signaling pathways mediated by Gaq/11 in primary cells and UM lines. As a first step, we will determine the baseline and UVA-evoked levels of Ca2+ and ROS, two important second messengers that control many signaling pathways downstream of Gaq/11. The results of these studies will significantly advance our understanding of how signal transduction pathways are altered in UM and will reveal novel potential targets for UM treatment.

References

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Key words

Uveal Melanoma, GNAQ, GNA11, Signal transduction.