Symposium: New concepts in dermatopharmacology

Mechanism driven approach to the prevention and treatment of basal cell carcinomas

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BASAL CELL CARCINOMAS (BCCs) are the most common type of human malignancy in the United States; more than one million Americans are diagnosed with BCCs each year. BCC risk directly correlates with exposure to environmental solar ultraviolet (UV) radiation. BCCs manifest sonic hedgehog (Shh) activation and Shh is among the most fundamental signal transduction pathways in embryonic development. Shh pathway activation occurs in both human and UVB-induced murine BCCs, and aberrant Shh signaling, due to inactivating germline mutations in Ptch, the repressor of this pathway, is associated with the rare, dominantly inherited disorder known as Nevoid Basal Cell Carcinoma or Gorlin syndrome. These patients develop large numbers of BCCs, in addition to developing various extracutaneous tumors such as medulloblastomas and rhabdomyosarcomas. Knowledge of the importance of Shh signaling in driving BCC pathogenesis, has led to the identification of small molecules that target different components of this pathway, including smoothened (Smo), Shh, and Gli-1. However, because the Shh signaling pathway is indispensable for development and tissue homeostasis, the safety of Shh inhibitors is an essential consideration for human use. Moreover, preclinical studies indicate that simply targeting the Shh pathway may not totally block the proliferation of BCC cells, suggesting that additional pathway(s) may contribute to drive BCC pathogenesis. Our approach has been to use murine models of BCCs to verify efficacious suppression of the growth of UVB-induced tumors by simultaneously inhibiting the Shh and Akt1 and mTOR pathways thereby implicating Akt1-mTOR signaling in BCCs development. Furthermore, we have shown that the Shh pathway directly regulates mTOR expression and that mTOR is a direct transcriptional target of SOX9, a transcription factor regulated by Gli-1. We have also shown that mTOR inhibition by rapamycin is only partially effective in reducing the growth of UVB-induced BCCs indicating the involvement of Akt1-dependent, but mTOR- independent, pathways that drive the growth of BCCs. Our goal is to develop mechanism-driven innovative approaches to the prevention and treatment of BCCs, the most common type of human malignancy. Indeed we are currently conducting clinical trials in patients with Gorlin syndrome using this approach.