MOLECULAR MECHANISMS OF SKIN DISEASES

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Three main forms of skin cancer, depending on the type of epidermal cells affected, are basal cell carcinoma, squamous cell carcinoma and cutaneous melanoma. Our research is focused on two of them, i.e. basal cell carcinoma (BCC) as the most common skin neoplasm, and melanoma as the most aggressive skin cancer. Although widespread and with increasing incidence, both were not well understood at the level of molecular pathogenesis until recently. Progress over the past decade has identified an array of molecular alterations in these neoplasms that may provide opportunities for new molecular therapeutics. A number of genetic alterations have been characterized, some of them involving gain-of-function changes in oncogenes, whereas others involve loss-of-function of genes that act as suppressors of tumor formation. The spectrum of changes differs among these tumor types. Major events in BCC onset and development are various alterations in the Sonic Hedgehog/Patched/Smoothened (SHH/PTCH/SMO) pathway, in particular PTCH1 loss-of-function, as well as gain-of-function by SHH, SMO and GLI. An important role in the genesis of melanoma plays CDKN2A locus on 9p21, encoding a cyclin-dependent kinase inhibitor p16 that acts to inhibit cell cycle progression in the G1 phase by binding and inhibiting CDK4/6 kinases. Loss of p16 leads to deregulated CDK4/6 action and to promotion of cell divisions. Involvement of p16 in melanoma development has been demonstrated either through loss of heterozygosity (LOH) for DNA markers within chromosome 9p21, or by mutational screenings of p16. We have been investigating the roles of both markers, PTCH and p16, in the pathogenesis of both cancers, cutaneous melanoma and basal cell carcinoma, and suggested the involvement of SHH/PTCH/SMO pathway by different mechanisms. Our particular interest in the role of SHH/PTCH/SMO pathway in various human cancers, which started with BCC and has more recently included melanoma, is motivated by the potential therapeutic use of small molecule antagonists that block the pathway. Another promising approach in melanoma research is the mitogen-activated protein (MAP) kinase pathway, which is affected in 40% to 60% of these carcinomas. The pathway is activated by mitogenic signaling from the membrane receptors towards the nucleus, which begins with the RAS, a small G protein, to protein kinase BRAF (an enzyme that adds phosphate groups to proteins to alter the substrate's function). The BRAF mutation (the V600E mutation) constitutively activates the pathway by increased kinase activity, leaving the 'growth' signal always turned on. It has been shown that RAS with oncogenic potential to induce melanoma in transgenic mice requires the active SHH/PTCH/SMO pathway. Additionally, it was found that RAS mediated by MAP and downstream AKT signaling regulates the nuclear localization and transcriptional activity of GLI1, which is a main citoplasmatic oncogene of the SHH/PTCH/SMO pathway in melanoma cells. All these recent findings suggest that an integrated approach to the RAS/AKT and SHH/PTCH/SMO pathways has a great and possibly synergic potential for future therapies of BCC and particularly of melanoma.