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Abstract 4744: Targeting nitric oxide signaling with nNOS inhibitors as a novel strategy for the therapy and prevention of human melanoma

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Abstract

The incidence of cutaneous melanoma (CM) has increased markedly over the past four decades although there have been some dramatic advances recently in the treatment of advanced melanoma. The development of novel therapeutic interventions blocking melanoma progression would be of high impact. Recently, our group has identified that neuronal NO synthase (nNOS) activated by UV radiation and growth factor plays an important role in melanoma progression, in parallel with generating constitutive NO stress. Knockdown of nNOS significantly reduced tumor growth and lung metastasis in vivo.

The newly developed nNOS inhibitors HHs (HH044 and HH045) exhibited potent anti-melanoma activity both in vitro and in vivo. The IC50s of HH compounds in human melanoma cells are less than 10 μM, which are comparable or even better than that of chemotherapeutic drug cisplatin (4.2μM and 14.3μM in A375 and Sk-Mel28 cells, respectively). Notably, the inhibition by HHs is more predominant in metastatic melanoma A375 cells compared to primary early stage Wm3211 cells, which supports our hypothesis that nNOS/NO signaling is more critical to melanoma progression than in the initiation phase. In a melanoma xenograft tumor model, we further determined the effects of HH044 and HH045 in tumor growth in vivo. Treatments with HH044 and HH045 (50mg/kg i.p for 21 days) significantly reduced the tumor size to 12% and 19% of control respectively with no apparent systematic toxicities observed. The body weight in treated mice was even moderately higher than the control’s. Taken together, these results are consistent with our hypothesis that targeting nNOS is an efficient and practicable approach for human melanoma therapy.