TRPM1 promotes tumor progression in acral melanoma by activating the Ca^{2+}/CaMKIIδ/AKT pathway

Abstract

Introduction:

Acral melanoma is a predominant and aggressive subtype of melanoma in non-Caucasian populations. There is a lack of genotype-driven therapies for over 50% of patients. TRPM1 (transient receptor potential melastatin 1), a nonspecific cation channel, is mainly expressed in retinal bipolar neurons and skin. Nonetheless, the function of TRPM1 in melanoma progression is poorly understood.

Objectives:

We investigated the association between TRPM1 and acral melanoma progression and revealed the molecular mechanisms by which TRPM1 promotes tumor progression and malignancy.

Methods:

TRPM1 expression and CaMKII phosphorylation in tumor specimens were tested by immunohistochemistry analysis and scored by two independent investigators. The functions of TRPM1 and CaMKII were assessed using loss-of-function and gain-of-function approaches and examined by western blotting, colony formation, cell migration and invasion, and xenograft tumor growth assays. The effects of a CaMKII inhibitor, KN93, were evaluated using both *in vitro* cell and *in vivo* xenograft mouse models.

Results:

We revealed that TRPM1 protein expression was positively associated with tumor progression and shorter survival in patients with acral melanoma. TRPM1 promoted AKT activation and the colony formation, cell mobility, and xenograft tumor growth of melanoma cells. TRPM1 elevated cytosolic Ca^{2+} levels and activated CaMKIIδ (Ca^{2+}/calmodulin-dependent protein kinase IIδ) to promote the CaMKIIδ/AKT interaction and AKT activation. The functions of TRPM1 in melanoma cells were suppressed by a CaMKII inhibitor, KN93. Significant upregulation of phospho-CaMKII levels in acral melanomas was related to increased expression of TRPM1. An acral melanoma cell line with high expression of TRPM1, CA11, was isolated from a patient to show the anti-tumor activity of KN93 *in vitro* and *in vivo*.

Conclusions:

TRPM1 promotes tumor progression and malignancy in acral melanoma by activating the Ca^{2+}/CaMKIIδ/AKT pathway. CaMKII inhibition may be a potential therapeutic strategy for treating acral melanomas with high expression of TRPM1.

Keywords

Acral melanoma; TRPM1; CaMKII; Ca^{2+} channel