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Coordination by Cdc42 of Actin, Contractility, and Adhesion for Melanoblast Movement in Mouse Skin.
Current biology : CB : DOI : S0960-9822(17)30065-9

Résumé

The individual molecular pathways downstream of Cdc42, Rac, and Rho GTPases are well documented, but we know surprisingly little about how these pathways are coordinated when cells move in a complex environment in vivo. In the developing embryo, melanoblasts originating from the neural crest must traverse the dermis to reach the epidermis of the skin and hair follicles. We previously established that Rac1 signals via Scar/WAVE and Arp2/3 to effect pseudopod extension and migration of melanoblasts in skin. Here we show that RhoA is redundant in the melanocyte lineage but that Cdc42 coordinates multiple motility systems independent of Rac1. Similar to Rac1 knockouts, Cdc42 null mice displayed a severe loss of pigmentation, and melanoblasts showed cell-cycle progression, migration, and cytokinesis defects. However, unlike Rac1 knockouts, Cdc42 null melanoblasts were elongated and displayed large, bulky pseudopods with dynamic actin bursts. Despite assuming an elongated shape usually associated with fast mesenchymal motility, Cdc42 knockout melanoblasts migrated slowly and inefficiently in the epidermis, with nearly static pseudopods. Although much of the basic actin machinery was intact, Cdc42 null cells lacked the ability to polarize their Golgi and coordinate motility systems for efficient movement. Loss of Cdc42 de-coupled three main systems: actin assembly via the formin FMNL2 and Arp2/3, active myosin-II localization, and integrin-based adhesion dynamics.

Juliette U Bertrand, Valérie Petit, Elke Hacker, Irina Berlin, Nicholas K Hayward, Marie Pouteaux, Evelyne Sage, David C Whiteman, Lionel Larue (2017 Feb 14)

UVB represses melanocyte cell migration and acts through β-catenin.
Experimental dermatology : DOI : 10.1111/exd.13318

Résumé

The exposure of skin to ultraviolet (UV) radiation can have both beneficial and deleterious effects: it can lead, for instance, to increased pigmentation and vitamin D synthesis but also to inflammation and skin cancer. UVB may induce genetic and epigenetic alterations, and have reversible effects associated with post-translational and gene regulation modifications. β-catenin is a main driver in melanocyte development; although infrequently mutated in melanoma, its cellular localization and activity is frequently altered. Here, we evaluate the consequence of UVB on β-catenin in the melanocyte lineage. We report that in vivo, UVB induces cytoplasmic/nuclear relocalization of β-catenin in melanocytes of newborn mice and
adult human skin. In mouse melanocyte and human melanoma cell lines in vitro, UVB increases β-catenin stability, accumulation in the nucleus, and co-transcriptional activity, leading to the repression of cell motility and velocity. The activation of the β-catenin signaling pathway and its effect on migration by UVB are increased by an inhibitor of GSK3β, and decreased by an inhibitor of β-catenin. In conclusion, UVB represses melanocyte migration and does so by acting through the GSK3-β-catenin axis. This article is protected by copyright. All rights reserved.

christyna ni, marie-sophie narzt, ionela-mariana nagelreiter, cheng feng zhang, lionel larue, heidemarie rossiter, johnnes grillari, erwin tschachler, florian gruber (2016 oct 13)
autophagy deficient melanocytes display a senescence associated secretory phenotype that includes oxidized lipid mediators.
the international journal of biochemistry & cell biology : doi : 51357-2725(16)30305-3

résumé

autophagy is a recycling program which allows cells to adapt to metabolic needs and to stress. Defects in autophagy can affect metabolism, aging, proteostasis and inflammation. Autophagy pathway genes, including autophagy related 7 (Atg7), have been associated with the regulation of skin pigmentation, and autophagy defects disturb the biogenesis and transport of melanosomes in melanocytes as well as transfer and processing of melanin into keratinocytes. We have previously shown that mice whose melanocytes or keratinocytes lack Atg7 (and thus autophagy) as a result of specific gene knockout still retained functioning melanosome synthesis and transfer, and displayed only moderate reduction of pigmentation. In cell culture the Atg7 deficient melanocytes were prone to premature senescence and dysregulation of nuclear factor (erythroid-derived 2)-like 2 (Nrf2) signaling. To elucidate the biochemical basis of this phenotype, we performed a study on global gene expression, protein secretion and phospholipid composition in Atg7 deficient versus Atg7 expressing melanocytes. In cell culture Atg7 deficient melanocytes showed a pro-inflammatory gene expression signature and secreted higher levels of C-X-C motif chemokine ligand -1,-2,-10 and -12 (Cxcl1, Cxcl2, Cxcl10, Cxcl12), which are implicated in the pathogenesis of pigmentary disorders and expressed higher amounts of matrix metalloproteinases -3 and -13 (Mmp3, Mmp13). The analysis of membrane phospholipid composition identified an increase in the arachidonic- to linoleic acid ratio in the autophagy deficient cells, as well as an increase in oxidized phospholipid species that act as danger associated molecular patterns (DAMPs). The secretion of inflammation related factors suggests that autophagy deficient melanocytes display a senescence associated secretory phenotype (SASP), and we propose oxidized lipid mediators as novel components of this SASP.

christine grill, lionel larue (2016 sep 25)
NRAS, NRAS, Which Mutation Is Fairest of Them All?
Résumé

In 28% of melanomas, NRAS is mutated in one of two hotspots: G12 or Q61. Phosphoproteomic analysis of primary human melanocytes transduced with G12 and Q61 showed different phosphorylation events in the phosphoinositide 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK) pathways. Surprisingly, NRAS(G12) modulates the PI3K pathway and overexpresses the kinase PIM2, whereas NRAS(Q61) is associated with the MAPK pathway and overexpression of CK2α.