candidate drug resistance gene due to the high CISs found only in the PLX4720-resistant tumors. Further characterization revealed four transposon sites in the first intron of ERAS, with an integration pattern signifying gene activation. The PLX4720-resistance conferring phenotype was confirmed in human melanoma cell lines ectopically expressing ERas. Further mechanistic studies revealed that ERAS inactivation of BAD (BCL2-associated agonist of cell death) through the PI3K/AKT pathway contributed to the observed PLX4720 drug resistance. The authors characterize a novel melanoma resistance gene identified from a transposon-mediated in vivo mutagenesis screen in mechanistic details. Future studies of the other candidate resistance genes may reveal novel mechanisms independent of MAPK or PI3K pathways. Most importantly, comparing candidates to gene expression profiles of treatment naïve and resistant human primary tumor samples can be an added filter to identify biologically relevant genes.

This report highlights the first example of the use of SB transposon-mediated mutagenesis in a murine melanoma model to identify genes that confer PLX4720 drug resistance. The authors also demonstrate a robust drug treatment regimen to evaluate drug efficacy in a GEM model that closely resembles the treatment course of melanoma patients. Future analysis of larger cohorts of tumors resistant to BRAF inhibition and/or other drug combinations may reveal more complex resistance mechanisms. In addition to identifying novel resistance mechanisms, the authors have demonstrated a powerful platform to test novel and more effective drug combinations in vivo to overcome PLX4720-mediated resistance.

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Ecad vitiliGONE

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Vitiligo is an acquired skin depigmentation disorder resulting from the selective loss of epidermal melanocytes. It is a common disease, which affects around 1% of the human population regardless of gender and which can appear at any age. Although vitiligo is not harmful nor contagious, it is often psychologically devastating for the patient. The pathology is generally classified into two major forms defined by the shape and the symmetry of the white skin patches. Non-segmental vitiligo, which represents the most common form, is characterized by bilateral and more or less symmetrical distribution of the skin discoloration. This form usually progresses throughout the life of the patient. In contrast, segmental vitiligo usually appears as a stripe on a segment of the body and can affect hair color as well. Segmental vitiligo often begins at an early age, and in most cases, the progression stops after a few years (Ezzedine et al., 2015).

The etiology of the disease is rather complex as it represents a spectrum of pathologies, all resulting in the loss of melanocytes. Although vitiligo is restricted to patches, allowing comparison of the affected skin with normal or prepathological surrounding tissue, the causes of this pathology are still under debate. Segmental vitiligo is suggested to be caused by peripheral nerve endings secreting substances that are presumably toxic for melanocytes. This theory is supported by the fact that in this type of vitiligo, the lesion is restricted to a specific dermatome. On the other hand, non-segmental vitiligo is induced by different mechanisms including autoimmunity and oxidative stress, which can either act independently or in synergy to induce the pathology, but all are eventually associated with an immune response against melanocytes. The central role of the immune system is reinforced by recent genomewide association study that identified genes regulating the immune response as susceptibility loci linked to vitiligo (Jin et al., 2010). The discoloration often starts in locations

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where the skin is exposed to conditions such as wounds, pressure, or repeated friction. This is called the Koebner's phenomenon and suggests that mechanical stresses are also an important component of the disease. The importance of these stresses is corroborated by weaker expression of adhesion molecules in keratinocytes in affected areas as well as by polymorphisms found in patients with mutations in discoidin domain receptor 1, a protein involved in melanocyte anchoring (Silva de Castro et al., 2010).

"misplaced melanocytes were more prone to apoptosis"

A recent paper by Roberto Gomes Tarlé et al. reports that a particular intronic variant of the CDH1 gene (E-cadherin) is associated with vitiligo susceptibility. In the cohort studied, this polymorphism was linked with autoimmune comorbidity. The important role of E-cadherin is confirmed by a thorough study from the Delmas group. In this paper, authors examined E-cadherin expression in biopsies obtained from healthy donors and non-lesional skin sections of patients with vitiligo. In comparison with healthy skin, E-cadherin expression decreased in melanocytes of patients while keratinocytes did not show any difference. Analysis of patient biopsies also revealed an infiltration of T lymphocytes, suggesting an inverse correlation between E-cadherin expression and the immune response. Strikingly, in patients with vitiligo, melanocytes were more frequently found in the suprabasal epidermal layer, even in non-lesional skin, possibly explaining the progressive loss of pigmentation. To study in a more assessable way the role of E-cadherin in vitiligo, the authors generated a melanocyte E-cadherin-deficient mouse model (ΔEcad mutant). Mouse tails have epidermal melanocytes in contrast to the hairy parts of the skin where melanocytes are localized in follicles. Tails of ΔEcad mutant did not develop white macules during their lifespan but exhibited lighter color compared to WT. A number of melanocytes contained large cytoplasmic vacuoles, as reported previously in patients with vitiligo (Tobin et al., 2000). However, when the tails of the mutant mice were subjected to repeated brushing, they developed vitiligo macules, hereby mimicking Koebner's phenomenon. The biopsies of the affected tails revealed a reduction in melanocyte numbers and some melanocytes were localized in the suprabasal layer, confirming the human biopsy observations. These results suggest that E-cadherin is required for melanocyte maintenance at the basal membrane and their resistance to mechanical stress. To assess what could lead to an E-cadherin decrease, Wagner and colleagues tested the effect of oxidative stress, a known cause of vitiligo. Treatment of cultured melanoma with H_2O_2 was sufficient to decrease E-cadherin expression, which could explain the chain of events happening during pathogenesis. Using reconstructed epidermis, the authors revealed that H_2O_2 induced melanocyte detachment when they express E-cadherin shRNA. Altogether, studies by Tavora Mira and Delmas' groups implicated E-cadherin in the etiology of vitiligo a mechanism involving by controlling melanocyte location and their resistance to mechanical stress.

The pathological detachment of melanocytes and their transepidermal elimination, as the primary event in vitiligo was observed over a dozen years ago (Gauthier et al., 2003), but no molecular mechanism could be identified. Dr Delmas' group provided an elegant model involving Ecad loss that recapitulates clinical observations. The proposed model is complementary to the clinical work of Dr Tavora Mira demonstrating a link between this adhesion protein and vitiligo occurrence.

These studies are adding a new piece to the puzzle, but the reason why melanocytes are disappearing is still unclear. Is E-cadherin loss sufficient to trigger melanocyte apoptosis? And if so, what is the cellular death signal? Another possibility is that E-cadherin downregulation leads to melanocyte detachment from the basal to the upper epidermal layer, and subsequently, melanocyte are simply lost due to skin desquamation. The presence of infiltrated T cells in affected skin, as suggested in Dr Delmas' paper, suggests that melanocytes are actively eliminated. It would be interesting to investigate whether the loss of E-cadherin is enough to recruit immune cells in the epidermis or alternatively whether the mislocation of melanocytes triggers an immune response. In both cases, it would be important to understand how the immune system becomes activated by changes in melanocytes and how the immune response occurs. Overall, Tavora Mira's and Delmas' group demonstrate that E-cadherin loss is a primary event in vitiligo, providing a new angle in the understanding of this enigmatic pathology.

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