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lymphocyte transformation tests. *Dermatology* 213:40–3

Karagiannidis C, Akdis M, Holopainen P, Woolley NJ, Hense G, Ruckert B *et al.* (2004) Glucocorticoids upregulate FOXP3 expression and regulatory T cells in asthma. *J Allergy Clin Immunol* 114:1425–33

Manome H, Aiba S, Tagami H (1999) Simple chemicals can induce maturation and apoptosis of dendritic cells. *Immunology* 98:481–90

Padial A, Posadas S, Alvarez J, Torres MJ, Alvarez JA, Mayorga C *et al.* (2005) Nonimmediate reactions to systemic corticosteroids suggest an immunological mechanism. *Allergy* 60: 665–70

Pan J, Ju D, Wang Q, Zhang M, Xia D, Zhang L *et al.* (2001) Dexamethasone inhibits the antigen presentation of dendritic cells in MHC class II pathway. *Immunol Lett* 76: 153–61

Rodriguez-Pena R, Lopez S, Mayorga C, Antunez C, Fernandez TD, Torres MJ *et al.* (2006) Potential involvement of dendritic cells in delayed-type hypersensitivity reactions to beta-lactams. *J Allergy Clin Immunol* 118:949–56

Steinman RM, Hawiger D, Liu K, Bonifaz L, Bonnyay D, Mahnke K *et al.* (2003) Dendritic cell function *in vivo* during the steady state: a role in peripheral tolerance. *Ann N Y Acad Sci* 987:15–25

Lack of Correlation between IGFBP7 Expression and *BRAF* Mutational Status in Melanoma

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TO THE EDITOR

Although the incidence of melanoma is still rising in many countries, the exact molecular pathogenesis for this tumor is unknown. Consequently, the publication of the study by Davies *et al.* (2002) reporting a high frequency of activating *BRAF* mutations in melanoma attracted much attention in the research community. Indeed, many independent groups have confirmed the high frequency of *BRAF* mutations in patients with melanoma; the mutation data on the COSMIC website (http://www.sanger.ac.uk/genetics/CGP/cosmic/) indicate that *BRAF* mutations were detected in 46% of melanoma patients ($n=3,634$), with BRAF V600E being the predominant mutation, found in 37.2% of the analyzed patients. However, given that in benign melanocytic nevi the frequency of *BRAF* mutations is similarly high (35% total mutations; 29.5% BRAF V600E; $n=830$, including 358 Spitz and blue nevi having a *BRAF* mutation frequency of ∼7%), *BRAF* mutations alone are not sufficient to initiate malignant melanoma. This thesis is sustained by experimental data showing that ectopic expression of constitutive active BRAF leads to senescence of primary cells (Michaloglou *et al.*, 2005). An autocrine/paracrine regulatory loop explaining this observation was recently described by Wajapeyee *et al.* (2008), who demonstrated the presence in normal cells of a basal expression of insulin-like growth factor–binding protein 7 (IGFBP7) that inhibits BRAF–MEK–ERK signaling and thereby restrains apoptosis. In nevi, BRAF mutations activating the MAP kinase pathway lead to an increased expression of IGFBP7, which not only inhibits BRAF–MEK–ERK signaling but also activates senescence. In contrast, in *BRAF*-mutated melanoma lesions, IGFBP7 expression is absent, enabling the cells to escape from senescence and thereby exhibit uncontrolled proliferation. Besides delivering the explanation for the observed effects of constitutive BRAF activation, the article by Wajapeyee and colleagues demonstrates a potential therapeutic application of this knowledge: treatment with recombinant

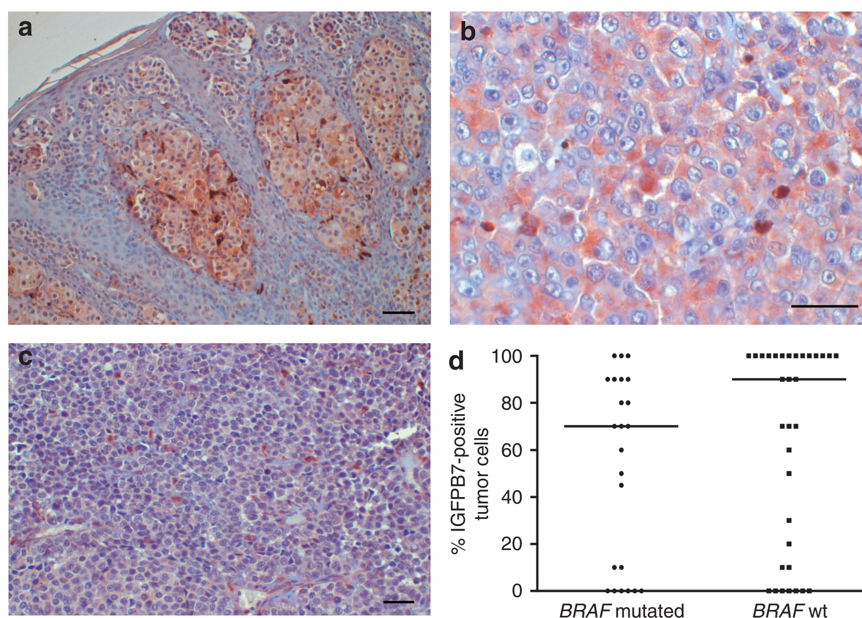

Figure 1. IGFBP7 expression in melanoma lesions. Primary tumors (**a**) or metastases (**b** and **c**) were stained with an anti-IGFBP7 antibody. Representative examples of lesions with *BRAF* mutations showing IGFBP7 expression (**a** and **b**) and with wt *BRAF* characterized by low IGFBP7 expression (**c**). (**d**) The results for all samples (34 wt and 23 *BRAF*-mutated lesions) are depicted. There is no significant difference between the two groups (Mann–Whitney test; $P=0.1609$). Bar = 100 μm.

Abbreviation: IGFBP7, insulin-like growth factor–binding protein 7

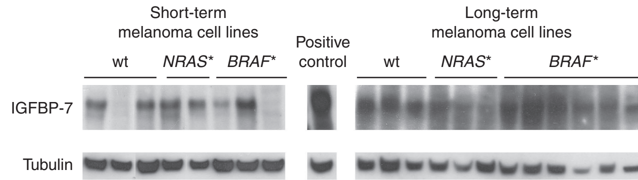

Figure 2. Lack of correlation between *NRAS/BRAF* mutational status and IGFBP7 expression in melanoma cell lines. The *NRAS/BRAF* status of cell lines was determined by sequencing. Lysates from these short- and long-term cultured melanoma cell lines were subsequently evaluated using western blot analysis for IGFBP7 expression.

IGFBP7 of *BRAF*-mutated melanoma cells triggered their apoptosis both *in vitro* and *in vivo* in a xenotransplantation model. Similarly, reactivation of IGFBP7 by DNA demethylation inhibits colon cancer cell growth *in vitro* (Lin *et al.*, 2008). With this therapeutic implication in mind, we further scrutinized the expression of IGFBP7 in melanoma. To this end, we stained formalin-fixed tissues obtained from 41 primary tumors and 16 metastases for IGFBP7 expression. Unlike Wajapeyee and colleagues, however, we did not detect a clear demarcation of IGFBP7 expression between *BRAF* wt (wild type) and mutated melanoma lesions (Figure 1). Indeed, although the frequency of IGFBP7-expressing cells is lower in *BRAF*-mutated melanoma lesions overall, the whole diversity of IGFBP7 expression from absent to present in 100% of tumor cells was observed in both wt and *BRAF*-mutated lesions ($P = 0.1609$; Mann–Whitney test). Accordingly, western blot analysis of short- and long-term cultured melanoma cell lines did not show any correlation between IGFBP7 protein expression and *BRAF* status either (Figure 2). Heterogeneous IGFBP7 expression could still be in accordance with the reported stringent IGFBP7/BRAF correlation, assuming a corresponding heterogeneity in the *BRAF* status. However, the homogeneous IGFBP7 expression in some of the *BRAF*-mutated tumors, as well as the lack of correlation for the cell lines, with one of them being hemizygote for the V600E BRAF mutation, argues against an obligatory downregulation of IGFBP7 expression in *BRAF*-mutated melanoma cells. Rather, it seems that loss of IGFBP7 expression is not the only way to overcome MAPK pathway–induced senescence. In this regard, dysregulation of the other 16 candidates detected by Wajapeyee *et al.* (2008), including BNIP3L, FOXA, and NF2, may be alternative mediators for overcoming senescence. Thus, detailed studies scrutinizing different *modi operandi* by which melanoma cells overcome BRAF-induced senescence are needed before the potential of IGFBP7 substitution for treatment of melanoma can be estimated.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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REFERENCES

Davies H, Bignell GR, Cox C, Stephens P, Edkins S, Clegg S *et al.* (2002) Mutations of the BRAF gene in human cancer. *Nature* 417:949–54

Lin J, Lai M, Huang Q, Ruan W, Ma Y, Cui J (2008) Reactivation of IGFBP7 by DNA demethylation inhibits human colon cancer cell growth *in vitro*. *Cancer Biol Ther* 7:1896–900

Michaloglou C, Vredeveld LC, Soengas MS, Denoyelle C, Kuilman T, van der Horst CM *et al.* (2005) BRAFE600-associated senescence-like cell cycle arrest of human naevi. *Nature* 436:720–4

Wajapeyee N, Serra RW, Zhu X, Mahalingam M, Green MR (2008) Oncogenic BRAF induces senescence and apoptosis through pathways mediated by the secreted protein IGFBP7. *Cell* 132:363–74

Indoleamine 2,3-Dioxygenase^{+} Cells Correspond to the BDCA2^{+} Plasmacytoid Dendritic Cells in Human Melanoma Sentinel Nodes

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TO THE EDITOR

Dendritic cells (DCs) have crucial roles in driving primary immune responses toward immunity or tolerance. While immature DCs prompt tolerance in peripheral tissues, mature DCs drive immunity in lymph nodes (Banchereau *et al.*, 2000). A particular subset of DC, however, is thought to have the ability to induce tolerance regardless of the maturation state (Gilliet and Liu, 2002).

Abbreviations: DC, dendritic cell; IDO, indoleamine 2,3-dioxygenase; pDC, plasmacytoid DC; SLN, sentinel lymph node; TLR, toll-like receptor