Melanoma pathogenesis and Nodal: a partial picture?

To the editor:

After reading the article by Topczewska *et al.*[1] implicating the role of the embryonic morphogen Nodal in melanoma pathogenesis, which I found to be extremely interesting, I was struck by the lack of scientific and historical perspective displayed by the authors. In particular, there is no mention or citation within their article of the possible expression of Cripto-1 in melanomas and its potential interactions with Nodal. Cripto-1 is an essential co-receptor for Nodal and is critical for Nodal's ability to function in a biological context through a Smad2/3 and FoxH1 signaling pathway. Nearly 20 years of research have demonstrated an important and essential role for Nodal in conjunction with Cripto-1 in early vertebrate development. In addition, the expression of Cripto-1 has been documented in a number of different types of human carcinomas, thereby exemplifying the importance of an early embryonic gene in the development of cancer where Cripto-1 may function to regulate epithelial-mesenchymal transition and tumor cell invasiveness[2,3]. Finally, there is evidence that Cripto can function through a Nodal-independent pathway via glypican-1 and src and that Nodal can function through a Cripto-1–independent signaling pathway during early development where it can act as a bone morphogenetic protein (BMP) antagonist. A more detailed examination as to the mechanism by which Nodal can regulate melanoma tumorigenesis and invasiveness is warranted.

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1. Topczewska, J.M. *Nat. Med.* **12**, 925–932 (2006).
2. Strizzi, L. *et al. J. Cell Physiol.* **201**, 266–276 (2004).
3. Ebert, A.D. *et al. Exp. Cell Res.* **257**, 223–229 (2000).

Topczewska *et al.* reply:

We agree with Dr. Salomon that it will be interesting to further explore the mechanisms by which Nodal regulates melanoma cell behavior. We did not intend to slight his work linking Cripto-1 to tumorigenesis and therefore cited his seminal paper[1] highlighting the expression of Nodal in testicular and breast carcinoma cells of epithelial origin. However, our paper is the first to report Nodal in melanoma, a mesenchymally derived tumor that does not undergo epithelial-to-mesenchmyal transition and contains fewer than 20% Cripto-1–positive cells. Thus, we did not wish to suggest the involvement of a Cripto-1–dependent pathway without more compelling evidence. A role for Cripto-1 in melanoma pathogenesis also remains uncertain because during development, Nodal apparently signals in part through stimulation—rather than inhibition—of a Cripto-1–independent bone morphogenetic protein (BMP) pathway[2]. The intent of our study was to use the zebrafish embryo as a biosensor for metastatic melanoma cells expressing a plastic, stem cell–like phenotype to modulate an embryonic microenvironment, which ultimately revealed Nodal as a mediator of melanoma plasticity and progression. As a corollary to our findings, we agree that it will be interesting to explore the possible role of Cripto-1 in Nodal-mediated tumorigenesis, tumor progression and metastasis.

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1. Adkins, H.B. *et al. J. Clin. Invest.* **112**, 575–587 (2003).
2. Ben-Haim, N. *et al. Dev. Cell* **11**, 313–323 (2006).

Challenges to the report of Nogo antibody effects in primates

To the editor:

The conclusion that Nogo-A–specific antibodies enhance sprouting and functional recovery after spinal cord lesions in primates is not supported by the data presented in a recent *Nature Medicine* article[1].

First, the control animal CP was excluded from certain statistical analyses on the basis of the incompleteness of its corticospinal tract lesion. However, 8 of 12 experimental subjects exhibited incomplete corticospinal tract lesions based on Supplementary Figure 1 of ref. 1. Further, two Nogo-treated animals, AA and AS, had partial corticospinal tract lesions similar to that of animal CP, yet were not excluded. This selective elimination of subjects was not conceptually or statistically valid and skewed the results. Second, spared ventral pathways can contribute to functional recovery. Supplementary Figure 1 indicates that there was slightly more ventral sparing in Nogo-treated animals compared to control-lesioned subjects, which could have favored functional recovery in the Nogo-treated group. Third,