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LETTER TO THE EDITOR

Cutaneous carcinosarcoma and the EMT: to transition, or not to transition? That is the question

Alberto Paniz-Mondolfi · Rajesh Singh · George Jour · Mandana Mahmoodi · A. Hafeez Diwan · Bedia A. Barkoh · Ronald Cason · Yve Huttenbach · Gustavo Benaim · John Galbincea · Rajyalakshmi Luthra

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To the editor:

We thank Dr. Zidar and Dr. Gale for their timely and detailed comments on our paper [1]. Indeed, epithelial-mesenchymal transition (EMT) is a multifaceted process driven by an intricate network of molecular mechanisms which to date remain incompletely understood, due to the extraordinary complexity of their regulation [2]. These processes include changes in cell adhesion and shape, gene expression, and extensive cross-talk between signaling pathways that create complex biochemical networks [2, 3], of which the final result in cancer is the development of mesenchymal-like cells with enhanced capacity for invasion, migration, and dissemination [3].

Even though some authors have proposed that phenotypic modulation in tumor progression is a reflection of genomic instability rather than an EMT-driven process [4], we strongly believe that there is compelling evidence suggesting a key role of EMT in the biology of tumor progression. As we proposed in our paper, primary carcinosarcomas of the skin are rare biphenotypic cutaneous tumors which simultaneously express both epithelial and mesenchymal elements, suggesting that in their development an EMT process might be involved [5]. We explored this possibility by assessing loss of E-cadherin expression and upregulation of vimentin expression, a pattern that is considered to be the hallmark of EMT changes in epithelial cells [5]. However, we do agree that more stringent criteria should be applied when assessing EMT-suggestive histological patterns.

As Zidar and Gale state, among the multiple criteria that should be assessed, the presence of spindle cell morphology is a sine qua non. Although different epithelial morphotypes of cutaneous carcinosarcoma exist (squamous cell or basal cell derived), the presence of a spindle cell component is obligatory and a feature of all cases we studied. In all cases we studied, β-catenin and E-cadherin were expressed in the cytoplasmic membrane of benign epithelium, while tumor cells showed decreased E-cadherin membranous expression along

A. Paniz-Mondolfi · A. H. Diwan · Y. Huttenbach
Department of Pathology and Immunology, Baylor College of Medicine, Houston, TX, USA

A. Paniz-Mondolfi (✉)
Departments of Biochemistry and Dermatopathology (SAIB/IVSS), Hospital Internacional & Universidad de Los Andes (ULA), Caracas/Barquisimeto/Mérida, Venezuela
e-mail: albertopaniz@yahoo.com

R. Singh · B. A. Barkoh · R. Cason · J. Galbincea · R. Luthra
Molecular Diagnostics Laboratory, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

G. Jour
Department of Anatomic Pathology, Memorial Sloan Kettering Cancer Center, New York, NY, USA

G. Jour
Department of Pathology, Memorial Sloan Kettering, Cancer Center, New York, NY, USA

M. Mahmoodi
Department of Dermatopathology, Miraca Life Sciences Research Institute & Tufts University School of Medicine, Boston, MA, USA

G. Benaim
Laboratorio de Señalización Celular y Bioquímica de Parásitos, Instituto de Estudios Avanzados (IDEA), Caracas, Venezuela

A. Paniz-Mondolfi
Department of Pathology and Laboratory Medicine, Laboratorio de Bioquímica, (SAIB/IVSS), Hospital Internacional de Barquisimeto, Avenida Intercomunal Barquisimeto–Cabudare con Avenida La Montañita, Urb. Las Mercedes, Cabudare, Estado Lara, Venezuela

with cytoplasmic and focal nuclear expression β-catenin [5]. Downregulation of E-cadherin represents a crucial molecular change in EMT as it reduces cell-cell adhesion and destabilizes epithelial architecture [3]. On the other hand, vimentin (the main intermediate filament of mesenchymal cells) was strongly expressed in the spindle cell component, a feature associated with the acquisition of a migratory phenotype and equally characteristic of EMT [3].

In a study published earlier by our group, ultrastructural analysis from transitional areas revealed a population of intermediate cells that showed thin 5-nm actin-sized cytoplasmic filaments with focal densities and dilated rough endoplasmic reticulum, characteristic of mesenchymal differentiation. The same cells contained mucin-filled cytoplasmic vacuoles and cytoplasmic tonofilaments with well-developed desmosomal attachments, typical of epithelial differentiation. These chimerical features are indicative of a mixed phenotype at the individual cell level [6]. Interestingly, in the deep mesenchymal areas in the invasive front of the tumors, all epithelial structures were lost (unpublished observations), which provides further morphological evidence of a phenotypic transition from epithelial to spindle cells. Even more interesting was the occurrence of isolated epithelial nests located deep in the dermis, not connected with or in continuity with overlying epithelium, which exhibited cell-cell adhesion structures suggestive of a reverse mesenchymal-epithelial transition.

Even though we were unable to assess the E-cadherin to N-cadherin switch, nor upregulation of important transcription repressors of the zinc finger Snail family (e.g., Snail, Slug), ZEB family (ZEB1/ZEB2), and/or basic helix-loop-helix family (Twist 1) as in the study on spindle cell carcinomas of the head and neck by Zidar et al. [1], we did observe downregulation of cytokeratin expression in spindle cell populations, which provided further evidence supporting EMT in this subset of cutaneous tumors.

Finally, the presence of specific PIK3CA and PDGFR-α mutations in two of our cases (with a basal cell epithelial component) is relevant since the PI3K/AKT signaling pathway as well as upregulation and/or activation of other tyrosine kinases have been implicated as key molecular promoters of migratory cell phenotypes in EMT and invasion [3]. PI3K/Akt signaling contributes to tumorigenesis by promoting cell survival and inhibiting apoptosis [3]. Also, Akt upregulates Snail and promotes EMT by modulating crucial components of the Wnt/ß-catenin pathway [3, 7], while PI3K concomitantly activates members of the Rho family small GTPases which also play an important role in EMT development [3]. In addition, platelet-derived growth factor (PDGF), as well as other components of its pathway, are selectively upregulated during EMT and intervene in several ways during late-stage tumor progression [8]. Assessing in our cases the expression of Snail, as well as other EMT-inducing transcription factors such as Twist, would be of pivotal importance in order to prove that PI3K/Akt activating mutations are involved in the mechanisms driving modulation of the epithelial-mesenchymal phenotype.

EMT is a highly dynamic process involving cellular and molecular events which vary in time as they are modulated by different micro-environmental contexts and ever-changing cell-conversion kinetics [2, 3]. As a consequence, further studies should include a combinatorial approach incorporating most importantly high-throughput studies which can allow resolving the molecular landscape and differential gene expression at any given time in order to elucidate the critical events of epithelial-mesenchymal phenotype conversion. Much has been learned about the mechanisms involved in EMT, but much remains to be elucidated, particularly in this rare subgroup of biphenotypic cutaneous tumors.

Conflict of interest The authors declare that they have no conflict of interest.

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