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Commentaries

"Cell identity" crisis: Another call for immediate action

Deilson Elgui de Oliveira [a,b,*], Cleiton Silva Marques [a], Victor Costa Losi [a]

[a] Viral Carcinogenesis and Cancer Biology Research Group (ViriCan) at Biotechnology Institute (IBTEC), São Paulo State University (UNESP), Alameda das Tecomarias, s/n, Botucatu, SP CEP 18607-440, Brazil
[b] Pathology Department at Botucatu Medical School, São Paulo State University (UNESP), Av. Bento Lopes, s/n, Botucatu, SP CEP 18618-970, Brazil

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Dear Editor,

We read with much interest the paper published in Cancer Lett. 360 (2015) 234–244 [1], which provides relevant data about the effects of the modulation of the store-operated Ca^{2+} entry process (SOCE) by the Latent Membrane Protein 1 (LMP1), the most studied oncogenic product of the Epstein–Barr Virus (EBV). Briefly, the authors reported that the inhibition of the boosting effect of EBV LMP1 on SOCE had a detrimental impact on cell migration, as well as angiogenesis and endothelial permeability *in vitro*. Furthermore, the mobilization of endothelial cell and vasculature invasion (elegantly assayed in zebrafish model), as well as the formation of distant metastases in Nude/SCID mouse by circulating disseminated LMP1-expressing cells was impaired by SOCE blockage. As a conclusion, the authors claim that LMP1-boosted SOCE contributes for the metastatic potential of nasopharyngeal carcinoma (NPC) cells, taking into account the assumed histogenetic origin of the cell lines used in their experiments.

The reported data strengthen the hypothesis that oncogenic viruses may impact cancer progression, and EBV-associated NPC is a very important model in this regard [2]. Nonetheless, the experiments were conducted with CNE1 and HNE2 cells, which show evidence to be HeLa derivatives [3,4], albeit regarded as EBV-negative NPC cells.

There are obvious shortcomings on drawing conclusions on pathogenesis of EBV-associated NPC based on results from these cell lines, and this issue is not limited to the above-mentioned paper: in a recent study published on another reputed journal, it was reported that the expression of the EBV LMP1 in several epithelial cell lines *in vitro* resulted in enrichment of cells expressing CD_{44}^{high}, a feature commonly associated with the cancer stem-cell phenotype (CSC). Moreover, the LMP1 induction of CSC traits was mediated by PI3K/AKT and mIR-21 activity, as well as PTEN suppression. The authors concluded that the results indicate a novel mechanism by which LMP1 expression contributes in the pathogenesis of EBV-associated NPC [5]. However, some of the study experiments were also conducted with the HeLa-contaminated cells, in this case CNE2 and HONE1 [3,4]. Worth to note, the NPC cell lines AdAH, NPC-KT, HONE-1, HNE-1 and HNE-2 were flagged as "potentially misidentified" by the International Cell Line Authentication Committee (ICLAC); additional data and biological samples from these cells are currently being requested to the scientific community [6] to determine their inclusion on the ICLAC database of misidentified cell lines [7,8].

Although cell identity issues are reported for some decades now, they continue to be largely neglected. The problem is truly epidemic in some settings: among 380 samples of cell lines from Chinese laboratories, contamination was reported in 1 out of 4, notably by HeLa cells [9]. Cell validation should be an ordinary practice nowadays, but this is not the case, even though accessible and reliable methods to perform it routinely are available. Indeed, cost-effective DNA profiling based on short tandem repeats (STRs) can be readily performed in any laboratory with PCR and capillary electrophoresis devices, and third-party services for cell validation are becoming more common everywhere.

Contaminated and misidentified cell lines generate unreliable and misleading data [10], compromise preclinical studies, and ultimately lead to waste incalculable amount of money and other resources. Hence, coordinated actions are vital: researchers must be committed not to generate data without validating each experimental cell lot, whereas funding agencies could increase the awareness by connecting access to grants to disclose quality control procedures for use of cultivated cells. On the publishing side, proof of cell authenticity must be a basic requirement for manuscript consideration. Hitherto, reviewers and editors must require that authors explicitly state how the cells used were validated. Adherence to these measures will minimize the "cell identity" crisis and improve significantly the invaluable role of cell culture for scientific and technological advances.

* Corresponding author. Faculdade de Medicina, Universidade Estadual Paulista (UNESP), Rua Bento Lopes, s/n – Distrito de Rubião Jr., Botucatu, SP CEP 18618-970, Brazil. Fax: +55 (14) 3815 2348.
E-mail address: elgui@virican.net (D. Elgui de Oliveira).

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