ORAL PRESENTATION



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Tax as a therapeutic target in ATL

Zeina Dassouki^{1,2}, Umut Sahin^{2,3,4}, Hiba El Hajj¹, Florence Jollivet^{2,3,4}, Youmna Kfoury¹, Valérie Lallemand-Breitenbach^{2,3,4}, Olivier Hermine⁷, Hugues de The^{2,3,4,5,6}, Ali Bazarbachi^{1*}

From 17th International Conference on Human Retroviruses: HTLV and Related Viruses Trois Ilets, Martinique. 18-21 June 2015

The HTLV-1 Tax transactivator initiates transformation in adult T-cell leukemia/lymphoma (ATL), a highly aggressive chemotherapy-resistant malignancy. The arsenic/interferon combination, which triggers degradation of the Tax on coprotein, selectively induces apoptosis of ATL cell lines and has significant clinical activity in Tax-driven murine ATL or patients. Yet, the role of Tax expression in maintaining the transformed phenotype and of Tax loss in ATL response is disputed and the molecular mechanisms driving degradation remain elusive. Here we demonstrate that ATL-derived or HTLV-1 transformed cells are addicted to continuous Tax expression, suggesting that Tax degradation underlies clinical responses to the arsenic/interferon combination. The latter enforces PML nuclear body (NB) formation and partner protein recruitment. In arsenic/ interferon-treated ATL-derived cells, Tax is recruited onto NBs, undergoes PML-dependent hyper-sumoylation by SUMO2/3, but not SUMO1, ubiquitination by RNF4 and proteasome-dependent degradation. Thus, the arsenic/interferon combination clears ATL through degradation of its Tax driver and could have broader therapeutic value by promoting degradation of other pathogenic sumoylated proteins.

Authors' details

¹Department of Internal Medicine, Faculty of Medicine, American University of Beirut, Beirut, Lebanon. ²Université Paris Diderot, Sorbonne Paris Cité, Hôpital St. Louis 1, Avenue Claude Vellefaux 75475 PARIS cedex 10, France. ³INSERM UMR 944, Equipe labellisée par la Ligue Nationale contre le Cancer, Institut Universitaire d'Hématologie, Hôpital St. Louis 1, Avenue Claude Vellefaux 75475 PARIS cedex 10, France. ⁴CNRS UMR 7212, Hôpital St. Louis 1, Avenue Claude Vellefaux 75475 PARIS cedex 10 France. ⁵AP-HP, Service de Biochimie, Hôpital St. Louis 1, Avenue Claude Vellefaux 75475 PARIS cedex 10, France. ⁶College de France, Place Marcelin Berthelot 75005 PARIS France. ⁷CNRS UMR 8147, Hôpital Necker, PARIS cedex 15, France.

* Correspondence: bazarbac@aub.edu.lb

¹Department of Internal Medicine, Faculty of Medicine, American University of Beirut, Beirut, Lebanon

Full list of author information is available at the end of the article



Published: 28 August 2015

doi:10.1186/1742-4690-12-S1-O20 Cite this article as: Dassouki *et al*.: Tax as a therapeutic target in ATL. *Retrovirology* 2015 12(Suppl 1):O20.

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