IJAE
Vol. 121, n. 1 (Supplement): 146, 2016
ITALIAN JOURNAL OF ANATOMY AND EMBRYOLOGY

Essential role for acid sphingomyelinase-inhibited autophagy in melanoma response to cisplatin

Davide Cervia [1] - Claudia Moscheni [2] - Chiara De Palma [2] - Matteo Giovarelli [2] - Patrizia Procacci [3] - Emilio Clementi [2] - Cristiana Perrotta [2]

[1] Università degli Studi della Tuscia, Department for Innovation in Biological, Agro-food and Forest Systems, Viterbo, Italia - [2] Università degli Studi di Milano, Department of Biomedical and Clinical Sciences "Luigi Sacco", Milano, Italia – [3] Università degli Studi di Milano, Department of Biomedical Sciences for Health, Milano, Italia

In advanced stages, melanoma is still a therapeutic challenge, despite the large number of chemotherapeutic regimens so far developed. Single drug chemotherapy is in many cases ineffective and combinations of chemotherapeutic drugs have demonstrated response rates only marginally higher, and at the cost of systemic toxicity. The new targeted therapies and immunotherapies have shown better efficacy and have supplanted chemotherapy as first-and second-line therapy. However, since melanoma cells eventually become resistant also to these novel therapies, the quest for new, more effective and possibly less toxic approaches is still open. The sphingolipid metabolising enzyme Acid Sphingomyelinase (A-SMase) has been recently shown to inhibit melanoma progression and correlate inversely to tumour grade [1]. We have investigated the role of A-SMase in the chemo-resistance to anticancer treatment using mice with melanoma allografts and melanoma cells differing in terms of expression/activity of A-SMase. Furthermore, as autophagy is a crucial determinant of the melanoma sensitivity to chemotherapeutic drugs, we have also investigated whether an action of A-SMase in autophagy can explain its role [2]. Melanoma sensitivity to chemotherapeutic agent cisplatin in terms of cell viability/apoptosis, tumour growth, and animal survival depended directly on the A-SMase levels in tumoural cells. A-SMase action was due to inhibition of autophagy through activation of Akt/mammalian target of rapamycin (mTOR) pathway. Treatment of melanoma-bearing mice with the autophagy inhibitor chloroquine restored sensitivity to cisplatin of tumours expressing low levels of A-SMase while no additive effects were observed in tumours characterised by sustained A-SMase levels. In conclusion A-SMase, affecting mTOR-regulated autophagy and playing a central role in cisplatin efficacy, is an attractive target in anti-tumour strategy for melanomas and our data encourage preclinical testing of the modulation of A-SMase levels/activity as possible novel antineoplastic strategy.

References

[1] Assi et al. (2015) Modulation of Acid Sphingomyelinase in Melanoma Reprogrammes the Tumour Immune Microenvironment. Mediators Inflamm. 2015:370482; doi:10.1155/2015/370482.
[2] Perrotta et al. (2015) The emerging role of acid sphingomyelinase in autophagy. Apoptosis. 20:635644; doi:10.1007/s10495-015-1101-9.

Keywords
A-SMase; melanoma; autophagy; mTOR; chemo-resistance.