Revisiting the cellular and molecular basis of melanoma chemoresistance: opportunities to innovative combination therapy

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Despite its low prevalence, melanoma incidence is increasing worldwide. Manageable when diagnosed in its early phases, advanced melanomas still pose a challenge for treatment. Enrollment of advanced melanoma patients in clinical trials are considered the standard of care in developed countries, as the results of treatments with conventional chemotherapeutic agents are considered poor. Understanding why melanoma cells are resistant to conventional therapy and devising ways of improving melanoma sensitivity towards chemotherapeutic agents may impact melanoma patient management in a cost-effective manner. Clinical protocols for palliative care of melanoma patients in Brazil include the use of dacarbazine (DTIC), which is metabolized into MTIC, and cisplatin (CDDP). We had evaluated the in vitro response of melanoma cell lines to CDDP and temozolomide (equivalent to MTIC). For cisplatin, the proteome of cell lines under treatment over time showed evidence for activation of the unfolded protein response (UPR) pathway and accumulation of the mitochondrial chaperone, prohibitin-1 (PHB1). The involvement of PHB1 in the response of melanoma cell lines to different treatments was then determined. Altogether, the results indicated that PHB1 accumulation favors melanoma cell survival to CDDP or temozolomide treatment, since melanoma cells got sensitized to death when de novo expression of PHB1 was inhibited using siRNA. The role of UPR in melanoma chemoresistance has also been addressed. Melanoma tissue specimens were analyzed regarding the expression and subcellular localization of GADD153, a transcription factor triggered by UPR. Although GADD153 was found in most of the melanoma specimens, it accumulated in the cytoplasm of melanoma cells, while it was found in the nucleus of nevi cells, which represent the benign counterpart of melanoma. We raised the hypothesis that melanoma cell survival could be then impaired with a sustainable increase in UPR, which in turn could lead to translocation of GADD153 to the nucleus, where the molecule would be a functional repressor of bcl-2 transcription. To test that, UPR was induced in melanoma cells using the cotranslational N-glycosylation inhibitor tunicamycin. UPR induction chemosensitized melanoma cells to CDDP, temozolomide and the V600E-BRAF inhibitor PLX4720. The mechanisms for chemosensitization include a decrease in bcl-2 expression and interference with autophagy. Also, PHB1 was induced by tunicamycin and PHB1 knockdown sensitized melanoma cells to tunicamycin induced cell death. At last, a key issue to the actual tumor response to chemotherapeutic agents resides in a homeostatic loop triggered by cell loss within tissues. There is increasing evidence that in tissues, cell death may trigger the growth of residual cells. The phenomenon, known as the Phoenix-Rising pathway, seems to occur in both irradiated tumor tissues and in tumors treated with chemotherapeutic agents, such as CDDP. Upon treatment, metabolism of membrane phospholipids leads to the formation of prostanooids (such as PGE2) and PAF, which in turn favor tumor growth and increased resistance to cell death. We had then shown that inhibition of PAFR-dependent signaling could improve response to either dacarbazine or CDDP in melanoma bearing mice. Revisiting the mechanisms for treatment failure with conventional chemotherapy will be useful for innovative combination treatment strategies that could be translated into patient benefits. Supported by FAPESP and CNPq.