A molecular triad in cancer: NPM1, RKIP and GRP78 candidates to biomarkers in tumor progression.


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INTRODUCTION: Proteomic approaches have been useful for the identification of aberrantly expressed proteins in complex diseases such as cancer. These proteins are not only potential disease biomarkers, but also targets for therapy. We found an interesting molecular triad expression variation of NPM1, RKIP and GRP78 proteins in patient and cell lines samples of glioma and melanoma.

METHODS: TM1 and TM5 melanoma cell lines were established after submitting a nontumorigenic melanocyte lineage (melan-a) to sequential cycles of forced anchorage impediment. Patient samples were collected during Genoma Clínico-FAPESP and U87MG, A172 and T98G cell lines were from ATCC. Proteomic analysis was performed by LC-SCX-RP of tryptic peptides after isobaric tagging and/or label free followed ESI-Q-TOF and MALDI-TOF/TOF-MS. Scaffold 3.6.5 was used for protein quantification and identification against Swiss-Prot database. Expression data were validated in a larger number of tumors by qRT-PCR, western blotting and immunohistochemistry.

RESULTS AND DISCUSSION: We reported that expression of nucleophosmin (NPM1) and GRP78 were increased and Raf kinase inhibitor protein (RKIP) decreased in glioblastoma multiforme (GBM). Proteomic analysis of melanoma cell lines showed the same pattern of expression of NPM1, GRP78 and RKIP found for our study in glioma. NPM and RKIP are involved in two signal transduction cascades known to contribute to the formation of glioma, i.e. RAS/RAF/MAPK and PI3K/AKT/mTOR. GRP78 plays a key role in cell survival and is a potent anti-apoptotic protein, involved in tumor progression, metastasis and resistance to therapy. In a large data set of GBM patients, both GRP78 and NPM1 genes were up-regulated and presented a tendency to shorter overall survival time.

CONCLUSION: Our hypothesis is that the pattern of these three proteins found in glioma and melanoma, may represent important biomarkers of tumor progression.

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