mTOR, p70S6K, AKT, and ERK1/2 levels predict sensitivity to mTOR and PI3K/mTOR inhibitors in human bronchial carcinoids

Teresa Gagliano, Mariaenrica Bellio, Erica Gentilin, Daniela Molè, Federico Tagliati, Marco Schiavon, Narciso Giorgio Cavallesco, Luigi Gaetano Andriolo, Maria Rosaria Ambrosio, Federico Rea, Ettore degli Uberti and **Maria Chiara Zatelli**

Abstract

Bronchial carcinoids (BCs) are rare neuroendocrine tumors that are still orphans of medical treatment. Human BC primary cultures may display resistance to everolimus, an inhibitor of the mammalian target of rapamycin (mTOR), in terms of cell viability reduction. Our aim was to assess whether the novel dual phosphatidylinositol 3-kinase (PI3K)/mTOR inhibitor NVP-BEZ235 is effective in everolimus-resistant human BC tissues and cell lines. In addition, we searched for possible markers of the efficacy of mTOR inhibitors that may help in identifying the patients who may benefit from treatment with mTOR inhibitors, sparing them from ineffective therapy. We found that NVP-BEZ235 is twice as potent as everolimus in reducing cell viability and activating apoptosis in human BC tissues that display sensitivity to mTOR inhibitors, but is not effective in everolimus-resistant BC tissues and cell lines that bypass cyclin D1 downregulation and escape G0/G1 blockade. Rebound AKT activation was not observed in response to treatment with either mTOR inhibitor in the 'resistant' BC cells. In addition to total mTOR levels, putative markers of the sensitivity of BCs to mTOR inhibitors are represented by AKT, p70S6K (RPS6KB2), and ERK1/2 (MAPK3/1) protein levels. Finally, we validated these markers in an independent BC group. These data indicate that the dual PI3K/mTOR inhibitor NVP-BEZ235 is more potent than everolimus in reducing the proliferation of human BC cells. 'Resistant' cells display lower levels of mTOR, p70S6K, AKT, and ERK1/2, indicating that these proteins may be useful as predictive markers of resistance to mTOR and PI3K/mTOR inhibitors in human BCs.