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p65BTK is a novel therapeutic target in p53-null drug-resistant colon cancers

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We recently identified p65BTK, a novel oncogenic isoform of Bruton tyrosine kinase abundantly expressed in colon cancer cell lines and tissues (Grassilli et al, Oncogene 2016) and showed that its inhibition affects growth and survival of colon cancer cells.

Here we report that p65BTK expression significantlyincreases with the stage and the grade of colon carcinoma and correlates with cancer progression. In addition, p65BTK is strongly expressed in organoidsderived from stem cells purified from patients' colon cancer tissues and in cancer stem cellsisolated from colon cancer specimens.

In vitro, p65BTK silencing (by siRNA or shRNA) and its inhibition by different specific inhibitors (Ibrutinib, AVL-292, RN486) sensitize drug-resistant p53-null colon cells and patient-derived organoidsto 5FU. At variance, blocking p65BTK does not restore the response of resistant cells to anti-EGFR receptor antibodies (panitumumab, cetuximab) and inhibitors (afatinib, poziotinib) or to bevacizumab. Conversely, p65BTK overexpression (but not overexpression of a kinase-dead mutant) protects p53-wt colon cancer cells from 5FU-induced cytotoxicity. Accordingly, p65BTK inhibition restores the apoptotic response to 5FU of drug-resistant p53-null colon cancer cellsvia imbalancing the anti-/pro-apoptotic ratio of Bcl-2 family members. In particular, p65BTK inhibition blunts 5FU-stimulated induction of the TGF-β pathway (anti-apoptotic) and induces E2F-mediated transcriptional regulation (apoptotic).

Finally, in xenograft experiments we confirmed that the combinationof 5FU with a BTK inhibitor (Ibrutinib) significantly reduced tumor volume in mice compared to the use of 5FU alone.

In conclusion, our data indicate that p65BTK targeting restores the apoptotic response to chemotherapy of p53-null drug-resistant colon cancer cells and suggest that the addition of BTK inhibitors to classic chemotherapy may represent a novel approach to bypass drug resistance.

Biography:

Dr. Grassilli received her Ph.D. degree from the University of Modena, Italy, and pursued her post-doctoral research at Thomas Jefferson University, Philadelphia and European Institute of Oncology, Milan, Italy studying the molecular mechanisms of apoptosis and their relevance in the response to chemotherapy. More recently, she co-founded Bionsil, a spin-off of the University of Milano-Bicocca, Italy, aimed at identifying and characterizing novel targets for molecular diagnosis and therapy of drug-resistant cancers. From 2014 she is Assistant Professor at the University of Milano-Bicocca where she continues her work on p65BTK, a novel Bruton's Tyrosine isoform previously identified as a new target of therapy in colon cancers.