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Src Inhibitors: a Synergic Help for Pancreatic Neuroendocrine Tumors Treatment

Livia Archibugi[1], Ilaria Passacantilli[1,2], Sara Calabretta[1,2], Gabriele Capurso[1], Gianfranco Delle Fave[1], Claudio Sette[2]

[1]Digestive and Liver Disease Unit, Faculty of Medicine and Psychology, University of Rome "La Sapienza", [2]Department of Biomedicine and Prevention, University of Rome "Tor Vergata". Rome, Italy

Context Pancreatic neuroendocrine tumors (pNETs) are becoming high in prevalence and have started showing a more aggressive behavior. Current therapies for advanced pNETs are inadequate as many patients develop primary or secondary resistance to mTOR (mammalian target of rapamicin) inhibitors, in part due to the activation of escape routes such as the PI3K/AKT pathway. SFKs (Src Family of Kinases) are overexpressed in pNETs and have a central role in controlling cell growth, adhesion and migration, also by regulating the mTOR pathway and the activation of the epithelial growth factor receptor in pNETs. SFK inhibitors are already safely used in patients with other tumors but have never been tested on pNETs. **Objective** To evaluate the use of SFK inhibitors on pNETs both alone and in combination with mTOR inhibitors. **Methods** Different dosages of dasatinib and bosutinib were tested in two human pNET cell lines, a pancreatic carcinoid (BON-1) and a somatostatinoma (QGP-1), either alone or in combination with the mTOR inhibitor RAD001 (everolimus). Src activation was assessed by monitoring Y416 phosphorylation. mTOR activation was assessed by testing rp-S6 and 4E-BP1 phosphorylation. Escape pathways were investigated through Akt and eIF4E phosphorylation. MTT and colony formation assays were used to evaluate cell proliferation. **Results** Dasatinib and bosutinib are effective at inhibiting Src activation and, when administrated together with RAD001, escape pathways are not activated. Extremely low dosages of RAD001 reduce cell proliferation when administered in combination with dasatinib or bosutinib. Colony formation assays show a strong reduction in colony number. BON-1 cells respond better than QGP-1 cells to treatments. **Conclusions** SFK inhibitors are promising new drug options for pNETs, as they reduce tumor cell proliferation when used in combination with RAD001. They allow to reduce RAD001 dosage, which may lower the risk of developing adverse effects in patients. Additional studies on animal models should be pursued to better assess their potential use in clinical therapies.