Anti-proliferative effects of Cetuximab and Trastuzumab in colorectal cancer cell lines
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Colon cancer is one of the most common human malignancies and a leading cause of death worldwide. In Europe around 250,000 new colon cases are diagnosed each year, accounting for around 9% of all the malignancies (Labianca R et al., 2010; Berrino F et al., 2007). Dysregulation of the signalling pathways induced through EGF receptors (ErbB/HER receptors) by their over-expression or constitutive activation can promote tumor processes (Lurje G et al., 2009), including colorectal cancer. Therefore, the ErbB/HER receptor family with their most prominent members EGFR and HER-2 represents validated targets for anti-cancer therapy. Cetuximab and trastuzumab are two monoclonal antibodies approved for treating, respectively, metastatic colorectal and breast cancer. Because the monotherapy with cetuximab in metastatic colorectal is often insufficient (Cunningham D et al., 2004), it is useful to develop complementary therapeutic strategies to enhance antibody efficacy. A possible approach is co-administration of inhibitors, targeting multiple members of the EGF receptor family. In this study we examined the effect of cetuximab and trastuzumab in combination using two human colon cancer cell lines as a model. We observed that the two drugs had a cytostatic effect and inhibited the proliferation of both the cell lines in a time- and concentration-dependent manner. However, the combination had lower efficacy on one cell line than the other, with growth inhibition of 31% in the former and 49% in the latter. This result was associated to specific changes in cell cycle distribution, while no apoptosis was observed. Chromosome copy number heterogeneity and aneuploidy in tumoral cell lines have been reported (Pellestor F et al., 1999). Our data deriving from the cell cycle analysis confirmed the aneuploidy and polyploidy in our cellular models and are useful to explain cellular response to the combination. We used fluorescent in situ hybridisation analysis to evaluate EGFR and HER-2 gene amplification status. Both the tumour cell lines resulted in an abnormal copy number for the two genes resulting from aneuploidy (polisomy of chromosome 7 and 17) which is not responsible for the difference in sensitivity to cetuximab and trastuzumab between the two cell lines. In order to understand and to improve the pharmacological efficacy of cetuximab and trastuzumab combination, it will be useful to elucidate the molecular mechanisms involved in their activity. This will allow to develop novel and interesting approaches to cancer therapy.

References

Keywords: Colon cancer, EGF receptors, cetuximab, trastuzumab.