The yeast *Saccharomyces cerevisiae* is sensitive to colorectal cancer routine treatment EGFR antibody Cetuximab

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Cetuximab/Erbitux® (Merk Sereno), a drug used in routine treatment of colorectal cancer and other malignant pathologies, is a monoclonal antibody against the Epidermal Growth Factor Receptor (EGFR). A frequent problem affecting the clinical use of Cetuximab is the lack of effectiveness deriving from frequent mutations in K-ras (1-3). A set of mutations in K-ras gene, KRAS c.35G>A (G12D), KRAS c.38G>A (G13D) in exon 2, and KRAS c.183A>T (Q61H) in exon 3, all implicated in the development of colorectal cancer, have been recognized as impeding Cetuximab's EGFR inhibitory action in human (1). Ras human genes have recognized counterparts in yeast, RAS1 and RAS2. The corresponding proteins belong to the PKA/cAMP MAPK pathway are involved in cell proliferation, in differentiation into hyphae and spores, in response to nitrogen starvation, and in carbon source regulation (4, 5). In opposition to Ras, yeasts do not have a recognized ortholog of EGFR. Nevertheless, yeast is sensitive to Imatinib, another drug that targets specifically EGFR in human cells (6). We generated recombinant yeast strains expressing human wild-type (wt) and mutated open reading frames (ORFs) of K-ras to use in the optimization of phenotypic tests appropriate for the assessment of cell sensitivity to Cetuximab. We observed that *Saccharomyces cerevisiae,* is sensitive to the treatment with this drug at identical concentration as human cell cultures. Moreover, the complementation of yeast deletions in RAS1 and/or RAS2 with wt or the above mentioned mutated forms of human K-RAS did not alter the response of the cells to the treatment. This suggests that the sensitivity of *S. cerevisiae* to Cetuximab is independent of the Ras/cAMP pathway. These results further indicate the existence of a paralog of EGFR protein in yeast cell surface. In view of these results, research focused on identifying the EGFR yeast counterpart, downstream effectors and target genes, and determining the correspondent Cetuximab/Erbitux® mode of action.

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