THERAPEUTICS

Cetuximab constricts conformational contortionist

Like other ERBB receptor tyrosine kinases, epidermal growth factor (EGF) receptor (EGFR) regulates cell proliferation, motility and differentiation, and its deregulation is implicated in a range of epithelial cancers. Ferguson and colleagues have used X-ray crystallography to determine how the EGFR inhibitor cetuximab — which is now used to treat advanced-stage colorectal cancer — physically blocks EGFR signalling.

EGFR signalling is triggered by the dimerization of EGFR receptors. Dimerization requires the binding of EGF ligands — which include EGF itself, transforming growth factor-α, amphiregulin and betacellulin — to the EGFR extracellular region. These ligands bind two separate extracellular domains of EGFR — domains I and III — and alter the conformation of the receptor so that the dimerization domain (domain II) is exposed. This effectively traps the receptor in a conformation that can dimerize with its neighbour.

Cetuximab is a human:mouse chimeric monoclonal antibody that binds with high specificity to the extracellular domain of EGFR and prevents receptor dimerization and signalling. Ferguson and colleagues determined the crystal structure of the cetuximab antigen-binding (Fab) fragment in complex with the soluble extracellular region of EGFR. They found that the Fab fragment binds exclusively to domain III of the receptor and covers an epitope that partially overlaps with the growth-factor-binding site, and this blocks the access of the ligand to this key region.

Cetuximab not only prevents ligand binding, but the heavy-chain (V_H) region of the antibody sterically prevents domain I of EGFR from adopting the conformation required for dimerization. Because the dimerization-competant conformation normally requires ligand binding, the importance of this conformational restriction is not yet clear. However, the authors point out that it could help to prevent potential ligand-independent modes of EGFR activation, perhaps through heterodimerization or homodimerization of EGFR when it or other ERBB receptors are aberrantly overexpressed.

The search for antagonistic ligand analogues to block EGFR signalling has not yet been successful, but the results of the present study raise the possibility that these analogues could be improved by fusing them to a more bulky molecule to enhance their potency. The authors also point out that the identification of the cetuximab epitope will be useful during screens for somatic mutations of EGFR that lead to increased or reduced sensitivity to the drug.

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References and links

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TRIAL WATCH

20-year outcomes

A 20-year outcome analysis for men with localized prostate cancer indicates that the mortality rates remain the same as those in the 15-year follow up, contradicting the findings of a similar study published last year.

A 20-year outcome study was published in 2004 by Johansson and colleagues on a population-based cohort of 223 men diagnosed with localized prostate cancer between 1977 and 1984. This study indicated a 3-fold increase in the prostate cancer mortality rate in the 49 men who were still alive after 15 years. In 1998, Albertsen and colleagues published a 15-year follow up of a similar population-based study in 767 men diagnosed between 1971 and 1984 who were either not treated, but monitored, or were treated by androgen withdrawal alone. Because all surviving patients continued to be assessed after this time, a 20-year study could be carried out to see if the prostate cancer mortality rates had changed.

Of the 767 men, 610 died before March 1 1997, 107 have died since and most of the 50 survivors have been contacted in the past 3 years. The outcome data were generated based on age at diagnosis and the Gleason score — a score based on the differentiation state of the prostate tumour cells in two significant areas on a biopsy specimen. The results follow the same trends as reported for the 15-year follow up — the prostate cancer mortality rate was 33 per 1,000 person years during the first 15 years (95% confidence interval (CI), 28–38) and 18 per 1,000 person years after 15 years (95% CI, 10–29) and were not statistically different.

The authors suggest that the difference between the two 20-year outcome studies could be due to histological classification and cause of death determination. Tumour histology remains a crucial diagnostic and prognostic tool. Histology sections can be obtained from surgical biopsy, which is required for the Gleason score (as used in this study), or can be obtained by needle biopsy and classified according to the World Health Organization system (as used in the Johansson study). Although both approaches are reliable, they might account for different grading of the severity of the disease in patients. Both studies also used different methods to identify cause of death — Johansson *et al.* relied on medical record review, whereas Albertson *et al.* relied on information on the death certificate — introducing another possible variable.

However, overall, the prostate cancer mortality rates are similar between the two studies. So, clinically, the findings of both studies indicate that men with well-differentiated localized tumours rarely require treatment, but those with poorly differentiated tumours treated with androgen deprivation alone will usually die from the disease, and a more aggressive regimen is warranted. The authors point out that only randomized controlled trials can address the many questions surrounding the efficacy of screening for prostate cancer and the best course of treatment for each individual patient. Such trials are currently underway in Sweden and the United States.

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