Cancer Biology & Therapy

ISSN: 1538-4047 (Print) 1555-8576 (Online) Journal homepage: https://www.tandfonline.com/loi/kcbt20

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To cite this article: Tomas Girbés, Lucia Citores, Jose Ferreras & Rosario Iglesias (2008) Killing cancer cells by targeting the EGF receptor, Cancer Biology & Therapy, 7:2, 243-244, DOI: 10.4161/cbt.7.2.5794

To link to this article: https://doi.org/10.4161/cbt.7.2.5794

Published online: 04 Feb 2008.

[Cancer Biology & Therapy 7:2, 243-244; February 2008]; ©2008 Landes Bioscience

Commentary

Killing cancer cells by targeting the EGF receptor

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Key words: OOSC, EGF receptor, chimeric toxins, saporin

Targeted toxins consist of a targeting polypeptide, usually a ligand or a monoclonal antibody, linked or fused to a toxin. In the case of monoclonal antibodies, the conjugates are called immunotoxins. When the targeting moiety is a cytokine, growth factor, transferrin or peptide hormone, the molecule is usually referred to as a chimeric toxin. The targeting protein or ligand directs the molecule to a cell surface receptor and the toxin moiety then enters the cell, inactivates protein synthesis and kills the cell. The toxins most commonly used for the construction of targeted molecules include Diptheria toxin and Pseudomonas aeurginosa toxin from bacteria and ricin, gelonin and PAP isolated from plants. A number of these targeted toxins have been clinically evaluated [1-4].

In this issue of *Cancer Biology & Therap*y, Bachran et al. analyze the effect of two chimeric toxins (SE and SA2E) consisting of the epidermal growth factor (EGF) and the plant protein toxin saporin towards an oral squamous cell carcinoma cell line (BHY) as well as on primary oral squamous cell carcinoma (OSCC) tumour cells. The toxic component in such chimeric toxins is saporin, a plant toxin which inhibits protein synthesis at ribosomal level,[5] and therefore must be internalized by the cell. To enhance the efficacy of the chimeric toxin in vivo and to reduce its side effects, the second construct (SA2E) contains a peptide adapter, which consists of a protein transduction domain and intracellular cleavage signals that conduct the toxin unidirectionally to the cytosol. While SE and SA2E were very effective in inhibiting BHY cells, fibroblasts remained unaffected. More importantly, after treating OSCCs from 28 patients with SE and SA2E, the authors observe a significant reduction in the number of OSCC colonies formed. The primary OSCC stem cell assay used in this study, which mimics the heterogeneity of real tumors, will be very useful for determining the potential usefulness of antitumor drugs before studies in vivo are initiated. Furthermore, saponin enhances the cytotoxicity of the chimeric toxin SA2E. These findings could contribute to the development of more specific anti-cancer drugs targeting the EFG receptor.

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Submitted: 01/24/08; Accepted: 01/28/08

Previously published online as a *Cancer Biology & Therapy* E-publication: www.landesbioscience.com/journals/cbt/article/5579

Commenary to: Christopher Bachran, Iring Heisler. Diana Bachran, Katrin Dassler, Matthias F. Melzig, Jürgen Ervens, Hendrik Fuchs. Chimeric toxins inhibit growth of primary oral sqaumous cell carcinoma cells. Cancer Biol Ther 2008; This issue.

Oral squamous cell carcinoma is a disease resistant to chemotherapy and radiotherapy treatments. The selective toxicity of the chimeric toxins on oral squamous cell carcinoma cells makes this molecule an interesting alternative for the treatment of this kind of cancer where surgical resection is the primary treatment. An opinion widely accepted is that one therapeutic approach will not be enough to trigger a substantial tumour reduction. Along this line, the current approaches combine chemotherapy and/or radiotherapy with new drugs and new targets [6,7]. One promising target is the epidermal growth factor receptor (EGFR). The EGF receptor belongs to the ErbB family of tyrosine kinase receptors (RTKs) and plays important roles in the diverse processes of proliferation and differentiation. The EGFR is expressed on the plasma membrane of most cell types, especially those of ectodermal origin. Binding of peptide growth factors of the EGF-family of proteins induces the formation of homodimeric and heterodimeric receptor complexes within the ErbB family. Upon formation of such complexes, the cytosolic domains are autophosphorylated and serve as docking sites for adaptor proteins and effectors that will further promote a complex network of intracellular signalling cascades which control cell survival, proliferation and inhibition of apoptosis. The activation of the receptor induces activation of the phospholipase Cγ (PLCγ) cascade, Mitogen-Activated Protein Kinase (MAPK) cascade, phosphatidylinositol-3 kinase (PI3K) cascade and Signal Transducers and Activators of Transcription proteins (STAT)[8,9]. Another pathway for signalling is the so called nuclear pathway in which the EFGR is internalised and localized to the nucleus[10].

EGFR has been found to be expressed and altered in a variety of malignancies and clearly plays a significant role in tumor development and progression, including cell proliferation, regulation of apoptotic cell death, angiogenesis and metastatic spread (Fig. 1). The mechanisms for the oncogenic conversion of EGFR in cancer include copy number amplification, structural rearrangements of the receptor, and activating mutations [11]. EGFR is overexpressed in many different types of solid tumors and is associated with metastasis and poor prognosis[12,13]. The high expression of such receptors on the tumor cell surface and the low expression in most normal tissues allow therapeutic approaches to be specifically targeted to abrogate EFGR function[14]. Among these are downregulation of EFGR expression, inhibition of EGFR downstream signalling and blockade of EGFR activation and phosphorylation.

A number of agents targeting EGFR, including specific antibodies directed against its ligand-binding domain (i.e. cetuximab, panitumumab, matuzumab) and small molecules inhibiting its tyro-

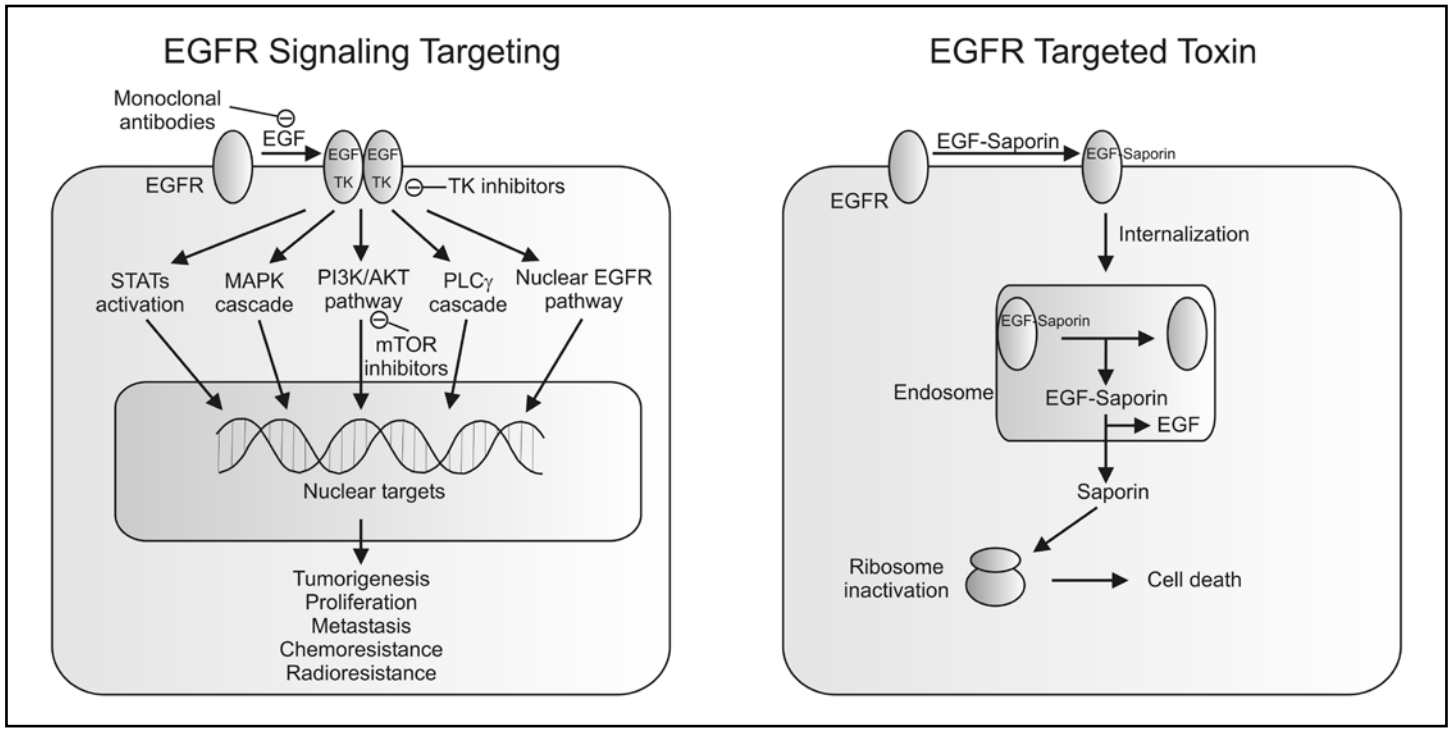

Figure 1. Strategies to target EGFR in tumor cells. A) EGFR signaling targeting: Mechanisms of action of EFGR in tumor cells. Activation of the signaling cascades often leads to tumorigenesis, tumour proliferation, metastasis, chemoresistance and radioresistance. Strategies to target EGFR include antibodies that bind to certain domains of EGFR preventing EGF binding (i.e. cetuximab, panitumumab, matuzumab) small molecules that inhibit intracellular signaling of the receptor by inhibiting its tyrosine kinase (TK) activity (i.e. gefitinib, erlotinib) and mTOR (mammalian target of rapamycin) inhibitors (i.e. rapamycin and derivatives). B) EGFR targeted toxin: The chimeric toxin binds to EGFR on a cancer cell, enters the cell by endocytosis and kills it.

sine kinase activity (i.e. gefitinib or erlotinib) are either in clinical trials or are already approved for clinical treatment [15-19] (Fig. 1). However, despite promising anticancer activity in clinical trials none of these approaches seems to be sufficient. Additional strategies to target EGFR include the use of immunotoxins and chimeric toxins obtained through conjugation of a cell-targeting moiety and a cytotoxic compound [20, 21] (Fig. 1). The endocytosis of the EGFR may be used to carry any kind of toxic agents including macromolecules like saporin as reported in the paper of Bachran et al. (Fig. 1). If further confirmed by testing in animal models, this may be a promising approach for combined therapy for patients with OSCC.

Acknowledgements

Supported by JCy L

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