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Target Oncogenic Receptors in Tumours, A Hot Topics Today

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Since the discovery of oncogenic receptor by George Zhu from oncogenic pml/RARa fusion in the origin of a specific APL and androgen/oncogenic androgen receptor signaling in hormonal tumorigenesis in 1989s, many studies are dedicated on their clinical targeting therapy. At present, thousands of publications and over 100 global journals are focused on this area targeting oncogenic receptor or oncogenic receptor (tyrosine) kinase in tumours [1-7]. The traditionally accepted view is that normal epidermal growth factor receptor (EGFR) is no tumorigenic [8].

Epidermal growth factor (EGF) consists of 53 amino acids residues and contains intramolecular disulfide bonds that are required for its biological activity [9-11]. EGF can stimulate or inhibit proliferation and differentiation in a wide variety of cells, e.g. Epidermal cells, corneal epithelial cells, fibroblasts, myofibroblasts, keratocytes and angiogenesis. EGF play a role in every tissue in the body during development and in the adult, the exact nature of this role is not clear. EGF interacts with a specific EGF receptor which located at the cell surface [12]. In recent, it has been suggested that EGF could be beneficial for burn, wound healing, diabetic foot ulcer, and provide an attractive perspective [13, 14, 15, 16].

In addition, cosmetic containing EGF could be effective to improve the plasticity, to remove wrinkle, to show whitening and anti-aging, and control of erythem amount and sebum amount on the human skin care. In this regard, George Zhu and Zhi QW in this field have successfully prepared a series of 68 bottles of Shampo liquid(New Washing) and 20 bottles of recombinant human EGF(rhEGF) spray,and 3 bottles of EGF- Silvadence ointment into market [11]. The initial results indicated that prepared rhEGF is safe and available in clinical wound healing and this may assist wound healing time.

On the other hand, tumour cells share oncogenic receptors [17-22]. The oncogenic receptor EGFRvIII is like this case. EGFvIII is the deletion of exons 2-7 in the EGFmRNA and correspond to cDNA nucleotides 275-1075, which encode amino acids 6-276 in the EGFR protein. Deletion of 801 bp within the extracellular domain of the EGFR leads to in-frame trunction of the normal EGFR protein, resulting in a 145-kda receptor [8]. Aggressive human glioma often express a truncated and oncogenic form of the epidermal growth factor receptor, known as EGFRvIII.

A series of EGFR mutations in human lung adenocarcinoma has been described [23, 24]. These mutations occur in four exons: substitutions for G719 in exon 18, in-frame deletions within exon 19, in-frame insertions within exon 20,and substitutions for L858 in exon 21. Up to now, gefitinib (Iressa) and erlotinib (Tarceva) are the first generation EGFR tyrosine kinase inhibitor (TKIs). Second generation EGFR TKI (afatinib and dacomitinib) were then developed more potent inhibitor. Moreover, gefitinib and erlotinib have a higher binding affinity for EGFR exon 19 deletion and exon 21 (L858R) substitution mutations than for wild-type EGFR.

Gefitinib and erlotinib inhibit the intracellular phosphorylation of EGFR tyrosine kinase,which blocks downstream signaling and EGF -dependent proliferation. Gefitinib and erlotinib were indicated for the treatments with metastatic non-small cell lung cancer (NSCLC) harboring EGFR exon 19 deletions or exon 21(L858R) substitution mutations. Drugs half-life were gefitinib 48 hours and erlotinib 36.0 hours respectively. Erlotinib is about 60% absorbed after oral administration and its bioavailability is significantly increased by food to almost 100%. As a third-generation EGFR TKI, Osimertinib binds to certain mutant forms of EGFR (T790M,L858R and exon 19 deletion) that predominate in NSCLC tumours who have progressed on or after first-line EGFR-TKI therapy [25, 26]. Therefore, approximately 10% of patients with NSCLC lung cancer patients containing activating EGFR mutation have been beneficial to dramatic clinically effective response to EGFR-TKIs.

Konduri and colleagues reported five patients with metastatic lung cancer whose tumors harbored EGFR fusion, most commonly RAD5, are recurrent in lung cancer [27]. Four of whom were treated with EGFR-TKI erlotinib with documented antitumor response for 5,6,8 and 20 months respectively. In our 2 patients with advanced lung cancers after oral gefitinib, we used gefitinib in keeping stable disease for 8+ months in a female patient with lung adenocarcinoma [28]. In the phase III trial of 419 patients with advanced T790M positive NSCLC following osimertinib vs platinum-based therapy,progression free survival in the osimertinib group was 8.5 months, compared to the platinum-based therapy group at 4.2 months [29].

The most promising,in Cuba, the CIMAvax-EGF vaccine trial is for people with stage IIIB or IV NSCLC who have been treated

previously by one line of chemotherapy. CIMAvax-EGF is a therapeutic cancer vaccine composed of human recombinant EGF in yeast (hu-recEGF) conjugated to the p64k Neisseria meningitides recombinant protein(recP64K)in Escherichia coli and Montanide ISA51 as adjuvant(Rodriguez,2016). At each immunization, patients received 2.4mg of hu-recEGF/recP64K/ Montanide. Four doses was the minimum number of injections at 50% of the patients reaching the GAR status.

Alternatively, patients who received at least four doses of CIMAvax-EGF had a significant effects on survival time. The vaccine induces antibodies against self EGFs that block EGF-EGFR interaction. In phase II clinical trial, mean survival was 19.47 months in 20 patients with good antibody responders(GAR),4.97 months in PARs(poor antibody responders)(n=18), and 8.52 months in 37 controls [30]. Long survival was found in all vaccinated patients(mean,18.53 months) compared to randomized unvaccinated controls(mean, 7.55 months) in the group aged < 60 years($p< 0.05$).

A phase III clinical trial in patients with advanced III/IV NSCLC, anti-EGF antibody titers was evaluated in 112 patients [31]. 89 patients was GAR and 24 patients with super-good responders (titers > 1:64,000 sera dilution). Patients with GAR criterion had a significant survival benefits. Mean survival time (MST) was 10.83 months in the vaccine arm versus 8.86 months in the controls. CIMAvax-EGF is a very safe drug that could be a feasible intervention for long-term control of those NSCLC patients with tumors depending on the EGF, capable of produce a rapid and durable response. This is encouraging.

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