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Commentary

Target Oncogenic Receptors in Tumours, Current Hot Spot Today

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Since the discovery of oncogenic receptor by George Zhu from oncogenic pml/RARa fusion in the etiology of a specific APL and androgen/oncogenic androgen receptor signaling in hormonal tumorigenesis in 1989s [1-7], many studies are dedicated on their clinical targeting therapy. At present, thousands of publications and over 100 global journals cited this scientific terminology 'oncogenic receptor and its target therapy or oncogenic receptor (tyrosine) kinase in tumours. 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 contain 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 is thought play a fundamental role in body tissue during development ad in the adult. EGF interact with a specific EGF receptor which located at the cell surface [12]. Recently, it has been indicated that EGF was found to exert its effects on superficial burn [13,14], wound healing, diabetic foot ulcer [15,16] and break a novel therapeutic strategy. In addition, cosmetics rich in EGF have the advantages of wrinkle removal, whitening, skin elasticity and anti-skin aging and in the amount of erythema and sebum control on skin care. In this regard, George Zhu and Zhi QW [11] in this field have successfully prepared a series of 68 bottles of Shampoo liquid (New Washing) and 20 bottles of recombinant human EGF (rhEGF) spray, and 3 bottles of EGF-Silvadene ointment into market. 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 [17,18]. The oncogenic receptor EGFRvIII is like this case. EGFvIII is characterized by the exons 2 - 7 deletion of EGFRmRNA, which is correspond to its cDNA nucleotides 275-1075 and encoding 6-276 amino acids in the EGFR protein. The 801 bp deletion in the extracellular domain of EGFR gene results in truncation of normal EGFR protein, leading to the form of a 145 kda receptor [8]. Progressive gliomas often had a truncated and oncogenic epidermal growth factor receptor, also oncogenic receptor EGFRvIII. Uptake of tumor cells derived microvesicles containing oncogenic EGFRvIII may alter the properties of endothelial cells and in relevance to tumor angiogenesis. Microvesicles containing EGFRvIII were released into the surrounding cells and blood of mouse tumors and could merge with the cytoplasmic membrane of cancer cells lacking this receptor. This process leads to the transfer of oncogenic activity [19]. tEVs (tumor-derived extracellular vesicles) had potential to induce cancer stem cells (CSCs) properties in normal tissue stem cells [20]. EGFvIII-containing microvesicles could stimulate the proliferation of malignant glioma cells, stimulate activity of MAPK and Akt pathway, triggered production of VEGF and increased anchorage-independent growth of tumor cells which was parallel by the increased phosphorylation of VEGFR2 [21]. *In vitro* in the absence of ligands 32D cells expressing high levels of 32D/EGFRvIII was capable of IL-3 independent proliferation. *In vivo* injection of 32D cells containing high level of EGFRvIII resulted in tumor formation in nude mice. However, the mice injected with 32D/EGFR or parent 32D cells had no tumors within 2 months [8]. In model mice expressing EGFR L858R in type II pneumocytes, transgenic mice developed atypical adenomatous hyperplasia, and tumors could be completely inhibited by gefitinib [22]. In our mice model, A subcutaneous nodule was clearly observed in the application of continuous EGF injection, while no sign of nodule was shown following intramuscle EGF injection within 20 days [11]. Overall, the data demonstrated EGFRvIII in a key importance in tumorigenesis.

A series of EGFR mutations in human lung adenocarcinoma has been described [23,24]. These mutations include G719 substitution in exon 18, in-frame deletions within exon 19, in-frame insertions within exon 20, and L858 substitution 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 mutation than for wild-type EGFR. Gefitinib and erlotinib also inhibit the intracellular phosphorylation of EGFR tyrosine kinase, which blocks downstream signaling and EGF-dependent proliferation. Gefitinib and erlotinib were therefore used for those advanced NSCLC harboring deleted EGFR exon 19 or mutated EGFR L858R. After oral use, 60% of erlotinib was absorbed and its bioavailability is considerably increased following food to near 100%. As a third-generation EGFR TKI, Osimertinib [25,26] 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. 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. It has been reported [27] that in 5 metastatic lung cancers with recurrent EGFR fusion such as oncogenic EGFR-RAD5 fusion, 4 of them has been demonstrated a dramatic response for 5, 6, 8 and 20 months following erlotinib inhibitor, 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]. Using comparative analysis of Osimertinib and Platinum- based treatment, in a phase 3 clinical trial of 419 patients with advanced T790M positive NSCLC, progression free survival in Osimertinib group was 8.5 months while the platinum-based group at 4.2 months [29].

The most promising, in Cuba, the CIMAvax -EGF vaccine is indicated for those patients with stage IIIB or IV NSCLC by undergoing one line of previous chemotherapy. CIMAvax-EGF consisted of recombinant human EGF in yeast (hu-rec EGF) conjugated to the Neisseria Meningitides recombinant p64 protein (rec p64k) in *Escherichia coli* and Montanide ISA51 as adjuvant agent [30,31]. At each immunization, patients received 2.4 mg of hu-recEGF/recP64K/Montanide. 50% of patients can reach the good antibody responders (GAR) status following four doses of injections. Alternatively, patients who received 4 doses of CIMAvax-EGF vaccine can display a long survival time. In general, CIMAvax-EGF can induce the immunogenicity of antibodies against self EGF, subsequently block EGF-EGFR interaction. In phase II clinical trial [30], 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. 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 [31], anti-EGF antibody titers was evaluated in 112 patients. 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. When compared to 8.86 months in the controls, mean survival time (MST) was 10.83 months in the vaccine arm. In summary, CIMAvax- EGF vaccine is a very safe and useful drug for prolonged control of those patients with advanced NSCLC tumors depending on the EGF, capable of displaying a dramatic efficacy. This is encouraging.

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