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Short communication

OVER EXPRESSED RECEPTORS AND STRATEGIES FOR TARGETING CANCER CASES PREVALENT IN NORTH EAST INDIA

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Abstract

Background*: There are various plant based compounds which have the potential to cure cancer but because of pharmacokinetic issues they are not used as potent anticancer drugs.* ***Objective:*** *This communication is aimed at highlighting the over expressed receptors and different strategies to target them in the treatment of various cancer cases which are prevalent in north east India.* ***Methods:*** *Extensive literature survey is been done to find out the different targeted drug delivery approaches which can help in improving their pharmacokinetic profile easily reaching the site of action and enhancing their therapeutic effects.* ***Results and Discussion****: North east India which is considered as a hotspot for various flora and fauna has many such potent anticancer compounds. There is an urgent need to explore these moieties with the novel strategies of cancer cell targeting.* ***Conclusion****: The solution to the increased cases of lung, ovarian or breast cancer among the population of this area may lie in exploration of its natural sources with these novel strategies.*

Keywords: Over expressed; Receptors; Lung cancer; Ovarian cancer; Breast cancer.

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Introduction

According to WHO the cancer mortality rate of India is 79 per 100,000 deaths accounting for over 6 percent of total deaths (WHO, 2015; WHO 3014) which is almost equal to those of high-income countries (WHO, 2011). By the end of this decade cancer mortality in India is supposed to increase to over 900,000 deaths (Takiar *et al.*, 2010). Lung cancer is one of the commonest cancers all over the world. In India, lung cancer constitutes 6.9% of all new cancer cases and 9.3% of all cancer related deaths in both sexes (ICMR, 2013). The northeast India reported the highest number of cancer cases in both males and females. Aizawl district in Mizoram reported the highest number of cases among males while Papumpare district in Arunachal Pradesh recorded the highest number among females (Malik *et al.,* 2015).Gynecological cancers are among the most common cancers in women and hence an important public health issue. Ovarian cancer has emerged as one of the most common malignancies affecting women in India and has shown an increase in the incidence rates over the years (Maheshwari *et al.*, 2016).

Cancer treatment is considered as a life-threatening course of therapy in addition to the symptoms of the disease itself because of its adverse-effects to the normal cells. To overcome this problem many approaches has been developed. Targeted delivery of anticancer drugs to cancerous cells is a growing area due to its capability to spare the normal cells. Many receptor molecules which are been over expressed in certain cancers are explored for the targeting of anticancer drugs. The principle of this approach is to concentrate the anticancer drugs specifically in cancer cells by conjugating drug-containing carriers with ligands against these receptors (Akhtar 2014). Though many drugs are developed, still there is a lots of known or unknown moieties still needed to be explored utilising this concept. The over

expressed receptors can also serve as a tool for early diagnosis of this disease, which is a major cause of failure to anticancer treatment.

Materials and Methods

Northeast India which is considered as a hotspot for various flora and fauna has many such potent anticancer compounds but unluckily not yet used because of their pharmacokinetic issues (Livney *et al.*, 2011). There is an urgent need to explore these moieties with the novel strategies of cancer cell targeting (Gupta *et al..*, 2017). The solution to the increased cases of lung, ovarian or breast cancer among the population of this area may lie in exploration of its natural sources with these novel strategies.

Different strategies for targeting the cancerous cells:

1. Receptor chemical and drug conjugates: In this approach the moiety having anticancer property is conjugated with the main chemical of the over expressed receptor. For example, vintafolide has been conjugated to folate for FRα targeting (Cheung *et al.*, 2016). Along with it imaging agents like Etarfolatide which is a ^{99m}Tc-based imaging agent has been administered in many patients suffering from lung, kidney, ovarian and other refractory solid tumors. Etarfolatide in combination with Vintafolide is used for pre selection of patients with overexpressed FRα tumors. The administration of folic acid prior to Etarfolatide infusion improves SPECT images (Yamada *et al.*, 2015).

2. Conventional small molecule drug: This strategy is aimed at targeting the over expressed receptors with small molecules having similar structure with that of the receptor's own chemical. Conventional anti-folate drugs like pemetrexed and methotrexate are transported by the high capacity Reduced Folate Carrier (RFC), which is ubiquitously expressed on both normal and tumor cells (Jackman *et al.*, 2004; Wang *et al.*, 2015).

3. Vaccines targeting the over expressed receptors: Autologous dendritic cells engineered with over expressed receptor mRNA show an immune response mediated by T-cells. Increased immunity has been reported in patients with ovarian cancer in comparison to healthy controls, suggesting that this may be a target for cell-based peptide immune-therapies (Basal *et al.*, 2009).

4. Genetically modified T-cell therapy: In this therapy chimeric antigen receptor (CAR) T cells are administered which is capable of recognizing over expressed receptors and ultimately trigger tumor cell killing (Cheung *et al.*, 2016).

5. Monoclonal antibodies: Monoclonal antibodies are capable of specifically recognising over expressed receptors leading to inhibition of downstream signalling events that cause tumor cell death. They can also mediate specific anti-tumor activity either by blocking cell signalling or by eliciting immune-mediated cell killing by engaging effector cells or complement (Cheung *et al.*, 2016).

6. Immune effector cell mediated antibody-dependent tumor cell killing: Antibodies linked with over expressed tumor cells with immune effector cells that bear the receptors itself, terminate effector cell activation and target neutralizing functions by engendering antibody-dependent effector cell-mediated cytotoxicity (ADCC), antibody-dependent effector cell-mediated phagocytosis (ADCP) and through complement-dependent cytotoxicity (CDC) activation (Cheung *et al.*, 2016).

Results and Discussion

A list of over expressed receptors in ovarian, lung and breast cancers and strategies for their treatment is given in Table 1.

Table-1: Over expressed receptors in ovarian, lung and breast cancers and strategies for treatment

Major receptor type	Specifically over expressed receptors	Cancer cell	Strategies
G-protein coupled receptors (GPCRs)	Bombesin receptor (BnR): This family consists of three closely related proteins, based on their amino acid sequence homology — i) the gastrin-releasing peptide receptor (GRP receptor) ii) the neuromedin B receptor (NMB receptor) and iii) the orphan receptor, BRS-3	Lung, breast and ovarian cancer	Conjugation of Bombesin with chemotherapeutic agents such as camptothecin, doxorubicin and paclitaxel (Akhtar 2014).
	Somatostatin receptors (SSTRs): Five subtypes of SSTRs have been described so far termed as SSTR 1–5. SSTR-2 is being widely used.	Lung and breast cancer	Conjugation of the anticancer drug taxol with the SSTR ligand octreotide (OCT) (Akhtar 2014).
Folate receptors (FRs)	FRα, FRβ and FRγ. FRα is the widely used and best studied, a cell surface glycosyl phosphatidylinositol-anchored glycoprotein that can internalize, bound folates and folate-conjugated compounds via receptor mediated endocytosis.	Lung, breast and ovarian cancer	1. Folate conjugates 2. Folate receptor specific monoclonal antibodies 3. Folate receptor specific T-cells 4. Anti-folate thymidylate synthase (TS) and glycinamide ribonucleotide formyl transferase (GARFTase) inhibitors (Shi *et al.*, 2015).
Epidermal growth factor receptor (EGFR)	EGFR family consists of four members: EGFR (or ErbB1, HER1), ErbB2 (HER2), ErbB3 (HER3) and ErbB4 (HER4).	Lung, breast and ovarian cancer	1. Monoclonal antibody (mAb) against EGFR 2. EGFR tyrosine kinase inhibitor (Altaha *et al.*, 2007).
Sigma receptors (SRs)	The two sigma receptors – S1R and S2R – were distinguished classically on the basis of their binding affinity for pentazocine and 1,3-di(2-tolyl)guanidine (DTG). Both bind pentazocine whereas only the latter binds with	Lung and breast cancer	SV119, an S2R ligand conjugated with anticancer drug (Akhtar 2014).

	DTG.		
Integrins	Among several subtypes formed by various combinations of α and β subunits, αvβ3 is of particular interest in selective drug targeting.	Ovarian cancer	Coated iron oxide NPs with copolymer and conjugated the near-infrared fluorescent (NIRF) dye IRDye800 and a cyclic Arginine- Glycine-Aspartic acid (RGD) containing peptide c(RGDyK) for integrin αvβ3 targeting (Akhtar 2014, Chen *et al.*. 2009).
Transferrin receptors (TfRs)	Two types of receptors (ubiquitously expressed TfR1 and TfR2 restricted to hepatocytes) only have been described so far. The transferrin receptor 2 (TfR2) shares a 45% identity and 66% similarity in its extracellular domain with TfR1.	Breast and ovarian cancer	Camp *et al.*. 2013, have delivered human wild type p53 protein (SGT53) (in combination with anticancer gemcitabine) bound with liposomal NPs, targeted to the transferrin receptor by a single-chain antibody fragment (TfRscFv) in an in vivo metastatic pancreatic cancer model.
Fibroblast growth factors (FGFRs)	There are four FGFR genes (FGFR1–FGFR4) that encode receptors consisting of three extracellular immunoglobulin domains (D1–D3), a single-pass transmembrane domain and a cytoplasmic tyrosine kinase (TK) domain	Breast cancer	Xiao *et al.*. 2010, developed a novel cationic liposomal nanocarrier for doxorubicin conjugated with human basic fibroblast growth factor (tbFGF) peptide, a modified peptide containing binding sites for the FGF2 receptor and part of heparin (Akhtar 2014).
Others	Follicle stimulating hormone receptors (FSHRs)	Ovarian cancer	1. Biotin-conjugated amphiphilic block NPs (Akhtar 2014). 2. Zhang *et al.*. 2009, developed a ligand called FSH33–53 that was derived from 33 to 53 amino acids of the FSH β chain. FSH33–53 was conjugated with NPs constructed from polyethylene glycol-poly(lactic acid) forming FSH33–NP complexes.

Conclusion

Exploration of the novel moieties against the specific receptor over expressing cancer cells may bring into light the specific protein involved in the DNA biosynthesis of ovarian, lung and breast cancer cells. The in-depth study of the internalization pathway of these compounds, their affinity for the over expressed receptors, identification of the protein of interaction inside the cells along with their role in cell signalling pathways may render novel class of anticancer compound as cost effective and target specific treatment specially for the group of patient that are not benefitted from the current conventional therapies.

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