We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800
Open access books available

122,000
International authors and editors

135M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

9

Emerging Therapies for Esophageal Cancer

Hajime Orita[1], Malcolm Brock[2] and Koichi Sato[1]
[1]*Juntendo University school of Medicine, Shizuoka Hospital, Department of Surgery*
[2]*Johns Hopkins University school of Medicine, Department of Surgery and Oncology*
[1]*Japan*
[2]*USA*

1. Introduction

This chapter will review the status of clinical and laboratory research exploring targeted therapies for treatment of esophageal cancer. Therapies that target specific pathways activated in cancers offer the potential for potent anti-cancer effects with minimal host toxicity. This review will not only summarize the status of targeted therapies currently being evaluated in clinical trials for treating esophageal cancer, but also discuss therapies that show promise in pre-clinical studies, including those that target metabolic pathways in cancer.

Esophageal cancer is the sixth most common cause of cancer mortality worldwide, and its incidence is increasing [1, 2]. Although there are different histologic variants of esophageal cancer **(Squamous cell and Adenoma carcinoma)** that have distinctive epidemiologic patters, the major risk factors (smoking, dietary factors) and many clinical features are similar among these histologic variants [3]. More than 90% of esophageal cancers – of all histologic variants - are diagnosed in late stage. In spite of new diagnostic and therapeutic approaches, esophageal cancer has poor prognosis, with 5-year survival rates between 10–13%.

Conventional treatment for esophageal cancer depends largely on stage of the tumor, typically including chemotherapy as well as surgery and radiotherapy. Standard agents include cisplatin, 5-fluoruracil, taxanes, irinotecan, and mitomycin C, but the inability of these agents to effectively treat most cases of esophageal cancer has provided an impetus for the recent attention that has been directed to therapeutics selectively targeting molecular pathways in cancer cells. Gene therapy, such as restoring p53 gene function, has also been explored [4], but because of the discouraging level of progress in this area, gene therapy will not be discussed in this chapter.

2. Targeting the EGFR signaling pathway

Epidermal growth factor receptor (EGFR) is one of the most commonly altered genes in human cancer, with alterations including overexpression, amplification, and mutation. Targeted inhibition of EGFR activity suppresses signal transduction pathways, affecting tumor cell proliferation and resistance to apoptosis. Small molecule tyrosine kinase inhibitors and monoclonal antibodies are among the most common EGFR-targeting agents and have been used clinically for treating various malignancies with EGFR mutations or

abnormal expression of the receptor. The outcomes of clinical trials using EGFR inhibitors will be summarized after a general discussion of the molecular biology of this target.

EGFR is a 170 KDa transmembrane glycoprotein situated on the cell surface, which is activated by binding of its specific ligands, including epidermal growth factor and transforming growth factor α (TGFα)[5]. . An EGF-specific receptor was first found on surface of fibroblasts in 1975 [6], but only relatively recently have mutations affecting EGFR been discovered to be involved in the development of cancers [7]. EGFR (also known as ERBB1/HER1) is a member of a family of receptor proteins that contains 3 other members: HER2/ERBB2, HER3/ERBB3, and HER4/ERBB4. All the receptor members of this family have an extracellular ligand-binding region or ectodomain, a single membrane-spanning region, and a cytoplasmic region that contains a tyrosine kinase domain. Binding of the ligand to the ectodomain initiates receptor homo- and hetero-dimerization, resulting in activation of the cytoplasmic tyrosine kinase and stimulation of intracellular signaling pathways. Gene amplification, mutation or structural changes of the receptor kinase can cause carcinogenesis, due to disregulation of cellular proliferation as well as characteristics that support cancer cell invasion and metastasis.

EGFR protein expression can be detected in about 30% to 70% of esophageal carcinomas [8, 9]. Similar to head and neck cancer squamous cell cancers (HNSCC), squamous cell carcinomas of the esophagus have very high frequency of elevated expression of EGFR (70-90%) [10, 11]. High levels of EGFR protein expression have been correlated with worse patient survival in both esophageal carcinoma and HNSCC, although the association has not been robust and results not consistent among various studies[12] [13] [14]. Moreover, a high EGFR gene copy number, which variably correlates with increased EGFR protein expression, also has been reported as a poor prognostic marker [15, 16]. Therefore, EGFR represents a rational target for therapeutics.

2.1 Monoclonal antibodies to target EGFR

There are several potential strategies to target the EGFR, most notably monoclonal antibodies (mAbs) and low molecular weight tyrosine kinase inhibitors (TKIs), which have both demonstrated clinical utility. mAbs bind to the extracellular domain of the receptor and compete with the natural ligands (TGF-αand EGF) binding to the receptor, therefore blocking activation of the receptor. By contrast, TKIs compete with ATP binding to the tyrosine kinase portion of the endodomain of the receptor and thereby abrogate the receptor's catalytic activity. Both strategies appear to be effective at blocking the downstream receptor-dependent signaling pathways, which include activation of MAPK, PI3K/Akt, and Jak/Stat.

In 1983, John Mendelsohn created the chimeric IgG1 Cetuximab('Erbitux', C225), the first epidermal growth factor receptor inhibitors (EGFR-I) [17]. In fact, cetuximab has been approved for the treatment of advanced colorectal cancer (CRC) over the last decade. Both single agent cetuximab as well as the combination with irinotecan have shown activity in patients with CRC [18, 19]. A second-generation EGFR-I, Panitumumab (ABX-EGF) is a fully human IgG2 mAb with high affinity for the EGFR[20].

Cetuximab has also shown efficacy in the treatment of non-small-cell lung cancer (NSCLC)[21-25]and locally advanced head and neck squamous cell carcinoma (HNSCC)[26, 27].

2.2 Clinical trial for targeting EGFR-I

Currently, several trials of EGFR-I with FOLFOX, FOLFIRI are demonstrating efficacy against CRC in various sites around the world [28, 29]. The side effects of IGFR-I therapy include skin rash, diarrhea, and hypomagnesaemia. Skin rash can be especially troubling, and this appears to be associated with depressive psychosis [30-32]. Biomarker analysis from several recent studies demonstrated that patients with KRAS mutated tumors are resistant to monotherapy with cetuximab or Panitumumab [33, 34]. Thus, benefits of adding EGFR-I to chemotherapy is limited to patients with wild-type (WT) KRAS in colorectal carcinoma [35, 36].

Several phase II trials for advanced esophageal cancer are ongoing throughout the world. One trial is the LLEDO G group (Paris) studying the effects of oxaliplatin, leucovorin and fluorouracil-when given together with Cetuximab and radiation therapy (NCT00578201). A second is being conducted at the National Cancer Institute (NCI), studying cetuximab in combination with cisplatin and irinotecan for treatment of patients with metastatic esophageal cancer, gastroesophageal junction cancer, or gastric cancer that did not respond to previous irinotecan and cisplatin (NCT00397904). Finally, a trial centered at Brown University is evaluating the rate of complete pathologic response as determined by surgical resection or post treatment endoscopy (for patients not undergoing resection) for the treatment regimen being tested (NCT00439608). While cetuximab administered as a single agent had minimal clinical activity in patients with advanced esophageal cancers, these ongoing phase 2 clinical trials of EGFR inhibitors in combination with other agents may define a role for these agents in the treatment [37, 38].

Interestingly, no KRAS mutations have been detected in esophageal cancers [39, 40], so mutations of this gene will apparently not cause resistance of esophageal cancers to EGFR-inhibitory therapy.

Shandong Cancer Hospital and Institute (NCT00815308) also studied to determine whether the treatment of locally advanced esophageal squamous cell carcinoma (ESCC) with cetuximab in combination with paclitaxel, cisplatin and radiation could improve clinical outcome. Unfortunately, the results were not encouraging. By contrast, the Hoosier Oncology Group (NCT00319735) investigating cetuximab combined with radiation found promising results. In this study, EGFR inhibitory agents enhanced radiation-induced apoptosis and inhibited radiation-induced damage repair. These interactions may represent the principle effects that contribute to the synergy between EGFR and radiation.

2.3 Tyrosine kinase inhibitors to target EGFR

Tyrosine kinase inhibitors (TKIs) are a class of small molecules that inhibit ATP binding within the tyrosine kinase domain, leading to inhibition of EGFR autophosphorylation and signal transduction. TKIs are now widely used in the treatment of lung cancers and are also being explored for treatment of esophageal cancers. Glivec was the first widely used TKI, used to treat myelogenous leukemia and gastrointestinal stromal tumors (GIST). A protein kinase inhibitor is a type of enzyme inhibitor that specifically blocks the action of one or more protein kinases. Hence, they can be subdivided or characterized by the amino acids whose phosphorylation is inhibited: most kinases act on both serine and threonine, the

tyrosine kinases act on tyrosine, and a number (dual-specificity kinases) act on all three. There are also protein kinases that phosphorylate other amino acids, including histidine kinases that phosphorylate histidine residues. They can interfere with the repair of DNA double-strand breaks [41]. TKIs are a class of oral, small molecules that inhibit ATP binding within the TK domain, which completely inhibits EGFR autophosphorylation and signal transduction [63].

There are a large number of TKIs directed to the EGFR family in clinical development for treatment of esophageal cancer. EGFR monoclonal antibodies (mAbs) bind to the extracellular domain of the receptor and compete with their ligands, therefore, blocking activation of the receptor. On the contrary, TKIs compete with ATP binding to the tyrosine kinase portion of the endodomain of the receptor and, thereby, abrogate the receptor's catalytic activity.

Gefitinib (Iressa®) and Erlotinib (Tarceva®) have been approved for treatment in non-small cell lung cancer (NSCLC). Several clinical trials have demonstrated an increase in progression-free survival in EGFR mutant lung cancer patients treated with these agents [42]. More recently, Gefitinib (Iressa®) has been evaluated in esophageal cancer in several phase 2 studies. Rodriguez, C. P.[43] demonstrated 80 advanced esophageal cancer patients for chemoradiotherapy (CRT) plus gefitinib (250 mg/d). Although gefitinib did not worsen CRT toxicity, maintenance therapy proved difficult.

Other study, Altiok S, Gibson MK [44] describe a short-term ex vivo assay to predict response to epidermal growth factor receptor (EGFR) targeted therapy (gefitinib) in adenocarcinoma patients. According to their pharmacokinetics research, after treated with gefitinib (250 mg/day) for 14 days, advanced esophageal adenocarcinoma were correlated with the gefitinib-mediated alteration in proliferating cell nuclear antigen (PCNA) expression, a marker of cell proliferation. PK studies demonstrated constant gefitinib concentrations during the treatment, confirming persistent exposure of target tissue to the drug at sufficient levels to achieve EGFR blockade.

Erlotinib (Tarceva®) is the second generation drug. Ilson, D. H.[45] evaluated 30 patients with measurable, metastatic cancer of the esophageal and gastroesophageal junction received 150 mg erlotinib daily. Erlotinib had limited activity in esophageal cancer (2 of 24(8%) partial responses were observed in the EGFR-positive and no responses were observed in the EGFR-negative cohort. Reponses were limited to patients who had squamous cell carcinoma (2 of 13 patients; 15%; response duration, 5.5-7 months). The time to tumor progression was longer in patients who had squamous cell carcinoma (3.3 months; range, 1-24 months) compared with patients who had adenocarcinoma (1.6 months; range, 1-6 months; P = .026). Therapy was tolerable with the expected toxicity of skin rash (grade 1-2, 67%; grade 3, 10%). and some protracted stable disease were observed in those with squamous cell carcinoma. Efficacy according to EGFR status could not be assessed given the rarity of EGFR-negative tumors.

Recently, Lapatinib (Tykerb), used in the form of lapatinib ditosylate, an orally active drug, starts for breast cancer and other solid tumors treatment [46]. It is a dual tyrosine kinase inhibitor which interrupts the HER2 growth receptor pathway[47]. It is used in combination therapy for HER2-positive breast cancer. It has been approved as front-line therapy in triple

positive breast cancer and as an adjuvant therapy when patients have progressed on Herceptin [48, 49]. Phase 1 trials are now ongoing for esophageal cancer. Alvarez H and Maitra A in Hopkins [50] analyzed small molecule inhibitors of Axl function. Axl is a receptor tyrosine kinase (RTK) with oncogenic potential and transforming activity. Blockade of Axl function abrogated phosphorylation of ERBB2 (Her-2/neu) at the Lapatinib residue, indicative of receptor crosstalk. Axl RTK is an adverse prognostic factor in esophageal cancer. The availability of small molecule inhibitors of Axl function provides a tractable strategy for molecular therapy.

3. Targeting the HER2 signaling pathway

Amplification and over-expression of HER-2/neu (c-erbB-2) in esophageal cancer has also been to predict a poor prognosis. Although recognition of gene amplification could be considered as a therapeutic target in esophageal cancer, there is actually a paucity of data regarding HER-2/neu amplification in esophgeal cancer and its implications for clinical management.

HER2/neu (also known as ErbB-2) exists on the cell surface and is a 185 KDa transmembrane glycoprotein with tyrosine kinase activity[51]. It is a member of the ErbB protein family, more commonly known as the epidermal growth factor receptor family. In 1985, this cell surface receptor of the tyrosine kinase gene family was identified and characterized by molecular cloning [52] .HER2 is a cell membrane surface-bound receptor tyrosine kinase and is normally involved in the signal transduction pathways leading to cell growth and differentiation. HER2 gene is relating the development and maintenance of heart and nerve system, and also cell proliferation and differentiation [53, 54]. However, ErbB receptors dimerise on ligand binding, and HER2 is the preferential dimerisation partner of other members of the ErbB family[55]. The HER2 gene is a proto-oncogene located at the long arm of human chromosome 17(17q21-q22)[52].

HER2/neu is a protein associated with aggressiveness in breast cancers. Approximately 30% of breast cancers have an amplification of the HER2/neu gene or overexpression of its protein product. Overexpression of this receptor in breast cancer is associated with increased disease recurrence and worse prognosis [56, 57]. Because of its prognostic role as well as its ability to predict response to trastuzumab (Herceptin), breast tumors are routinely checked for overexpression of HER2/neu same as hormone receptors. HER2 is also overexpressed in other types of cancers, including 25–30% of ovarian cancers [58], 35–45% of pancreatic carcinomas[59, 60], and in 30–80% of esophageal adenocarcinoma [61, 62], and squamous cell carcinoma [63-65].

A drug targeting HER2/neu is the monoclonal antibody trastuzumab (Herceptin). Trastuzumab is effective only in cancers where the HER2/neu receptor is overexpressed. In fact, trastuzumab was clinically shown to have survival benefit in patients with HER-2–overexpressing breast cancer with metastasis [66, 67]. One of the mechanisms of how trastuzumab works after it binds to HER2 is by increasing p27, a protein that halts cell proliferation [68].

The results of a study combining trastuzumab with cisplatin in HER2 positive untreated patients with gastric or gastro-esophageal junction cancer have recently been presented [69].

In this study, capecitabine plus cisplatin or fluorouracil plus cisplatin was given every 3 weeks for six cycles or chemotherapy in combination with intravenous trastuzumab (NCT01041404). 594 patients were randomly assigned to study treatment (trastuzumab plus chemotherapy, n=298; chemotherapy alone, n=296), of whom 584 were included in the primary analysis (n=294; n=290). Median overall survival was 13.8 months (95% CI 12-16) in those assigned to trastuzumab plus chemotherapy compared with 11.1 months (10-13) in those assigned to chemotherapy alone (hazard ratio 0.74; 95% CI 0.60-0.91; p=0.0046). The most common adverse events in both groups were nausea, vomiting, and neutropenia. Rates of overall grade 3 or 4 adverse events (201 [68%] vs. 198 [68%]) and cardiac adverse events (17 [6%] vs. 18 [6%]) did not differ between groups. The authors concluded that Trastuzumab in combination with chemotherapy can be considered as a new standard option for patients with HER2-positive advanced gastric or gastro-esophageal junction cancer.

4. Angiogenesis inhibitors

Agents that inhibit vascular endothelial cell growth factor (VEGF) and the angiogenesis process have also attracted considerable interest for treatment of a variety of cancer types. VEGF is overexpressed in 30%–60% of patients with esophageal cancers. Bevacizumab, a recombinant humanized mAb to VEGF, is the most widely studied anti-angiogenesis agent. Bevacizumab is still undergoing clinical evaluation for esophageal cancer treatment, and this approach could represent an important addition to the treatment of this disease.

Vascular endothelial growth factor (VEGF) is a glycoprotein important for regulating vasculogenesis and angiogenesis. VEGF was first isolated in 1983 from mouse ascites[70] and functions to create new blood vessels for restoring the oxygen supply to tissues when blood circulation is inadequate. VEGF is activated by binding of its ligands VEGFR, leading to stimulation of cell division and differentiation. There are five members of the human VEGF family: VEGF-A (referred to in this chapter as VEGF), VEGF-B, VEGF-C,VEGF-D and placental growth factor (PlGF). In addition, multiple isoforms of VEGF, VEGF-B and PlGF are generated through alternative splicing of pre-mRNA.1 The VEGF family ligands interact with the receptor tyrosine kinases VEGF receptor-1 (VEGFR1), VEGFR2 and VEGFR3. VEGF family interaction with VEGFRs is also regulated by the non-enzymatic co-receptors neuropilin (Nrp)-1 and Nrp2.1. Bevacizumab binds VEGF-A, and inhibit function of VEGFR1, VEGFR2 and Nrp-1.

VEGF is overexpressed in 30%–60% of esophageal cancer tumors, and several studies have demonstrated a correlation among high levels of VEGF expression, advanced stage, and poor overall survival in patients undergoing a potentially curative esophagectomy [96–99]. One recent study suggests that the activation of the EGFR-pathway contributes to angiogenesis in esophageal adenocarcinoma by different mechanisms, including upregulation of VEGF and Neuropilin-1 expression [38]. In another study, Kulke and others found no significant association between VEGF expression and treatment response or overall survival [71]. This discrepancy may be in part explained by the potential induction of VEGF and increased angiogenic activity that may occur with the delivery of preoperative chemoradiotherapy. The treatment-induced development of more aggressive and resistant tumor phenotypes might weaken potential associations among pretreatment VEGF levels, treatment response, and overall survival.

Bevacizumab is a monoclonal antibody that binds to all isoforms of human VEGF and thus functions as a direct angiogenesis inhibitor. This drug has found use in combination therapy for colorectal cancer, with reported survival benefit when used in combination with irinotecan-, oxaliplatin- and 5-fluorouracil-based chemotherapy [38–41]. Bevacizumab has several severe side-effects when used for treatment of colorectal cancer, most notable intestinal perforation, which occurs at a frequency of somewhat less than 5 %. While emergency surgery can rescue patients with colon perforations, esophageal perforations would most likely be lethal to patients, suggesting that this drug will need to be used carefully in patients with esophageal cancers.

5. Metabolic pathways as targets for cancer therapy

Over the past decade, there has been increasing interest in cancer metabolism pathways as targets for cancer therapy. Two potential therapeutic strategies will be discussed with respect to esophageal cancer therapy: first, the potential role of metformin, a drug used for treatment of diabetes, and second the potential role of inhibitors of fatty acid synthase. Metformin is likely to be investigated at a clinical level soon, since this drug is widely available and has an established safety profile. While inhibitors of fatty acid synthase still require pre-clinical development, studies to date provide encouragement that this metabolic pathway could offer a new target for esophageal cancer therapy.

5.1 Metformin for cancer treatment

As a background for testing metformin in treatment of esophageal cancer, it should be noted that type 2 diabetes, is associated with significantly higher risks of developing certain types of cancers and with increased mortality from those cancers [72-74]. Insulin resistance, hyperinsulinemia, oxidative stress, advanced glycation end products, and chronic low-grade inflammations have all been considered to explain the association between diabetes and high cancer incidence. While gastroesophageal reflux and high body mass index (BMI) are well established risk factors [75-77] for esophageal cancers, it has also reported that diabetes is associated with substantial and significant increase in risk of esophageal adenocarcinoma [78-82].

Effective treatment of diabetes might favorably affect cancer incidence and mortality [83-85]. Since the 1960s, metformin (a biguanide) has become the first line anti-hyperglycemic agent in type 2 diabetes (T2DM) treatment worldwide[86], and a large number of observational studies have reported a reduced incidence of neoplastic disease in diabetic patients treated with metformin [87, 88]. It is generally thought that metformin suppresses gluconeogenesis in the liver, leading to decreased production of insulin, a potential cancer cell growth factor. In addition, by activating the enzyme AMPK (AMP activated protein kinase), skeletal muscles are induced to take up glucose from the blood. Moreover, by activating AMPK, metformin inhibits the mammalian target of rapamycin complex 1 (mTORC1) resulting in decreased cancer cell proliferation. Concomitantly, metformin induces activation of LKB1 (serine/threonine kinase 11), a tumor suppressor gene, which is required for the phosphorylation and activation of AMPK [89, 90].

The new encouraging experimental data supporting the anti-cancer effects of metformin urgently require further clinical studies in order to establish its use as a synergistic therapy

targeting the AMPK/mTOR signaling pathway. Although few studies have been performed to date, a retrospective study performed in Taiwan evaluating 800, 000 people found that diabetic patients without any drug treatment had twice the level of gastrointestinal cancer incidence (gastric, colorectal, hepatic, pancreatic and esophageal cancer) as metformin-treated diabetics. The authors of this study [78] proposed a metformin dose of 500 mg/ day for a significant decrease in cancer incidence.

Encouraging findings have also been reported in retrospective studies of breast cancer neoadjuvant chemotherapy for locally advanced (inoperable) breast cancer. This treatment has become an accepted alternative to adjuvant chemotherapy in operable early-stage breast cancer, because it allows breast conservation. Importantly, diabetic patients with breast cancer receiving metformin and neoadjuvant chemotherapy were found to have a higher pCR(Pathologic Complete Response) rate than diabetics not receiving metformin [91].

The breast cancer data is particularly relevant to the esophageal cancer situation, because neoadjuvant therapy (combinations of chemotherapy and radiotherapy) is also performed to reduce tumor size before surgery for advanced esophageal cancer. While no data is available for metformin effects in esophageal cancer neoadjuvant therapy, it certainly would be important to evaluate responses retrospectively as well as consider metformin use in non-diabetic patients for esophageal cancer treatment.

Interestingly, Hirsch H et al [92] reported that metformin selectively kills cancer stem cells in four genetically different types of breast cancer. The combination of metformin and a well-defined chemotherapeutic agent, doxorubicin, kills both cancer stem cells and non–stem cancer cells in culture. Furthermore, this combinatorial therapy reduces tumor mass and prevents relapse much more effectively than either drug alone in a xenograft mouse model. These results provide further evidence supporting the combination of metformin and chemotherapeutic drugs to improve treatment of patients with cancers, including esophageal cancer.

5.2 Fatty acid synthase as a target for cancer treatment

It is well-known that anaerobic metabolism predominates in many tumors, and this type of metabolism causes lipid combustion and beta oxidization. Lipids are made from triglyceride and fatty acids by the enzyme, fatty acid synthase. Fatty acid synthase (FAS) is highly expressed in many human cancers. [93]. Because fatty acid synthesis expends energy, it seems reasonable to expect that high FAS activity confers some survival or growth advantage to human cancer.

In esophageal cancer (both squamous cancers and adenocarcinomas), FAS is expressed at very high levels similar to other cancers [94, 95], and high expression is also seen in Barrett's esophagus with dysplasia [96, 97]. (Figure1) It appears that increased expression of FAS is associated with neoplastic transformation and is not typical of esophageal glandular epithelium in general [98]. Our recent study found that esophageal cancers (and likely high-grade precursors) that express high levels of FAS could potentially be treated by therapy directed to inhibit this enzyme.

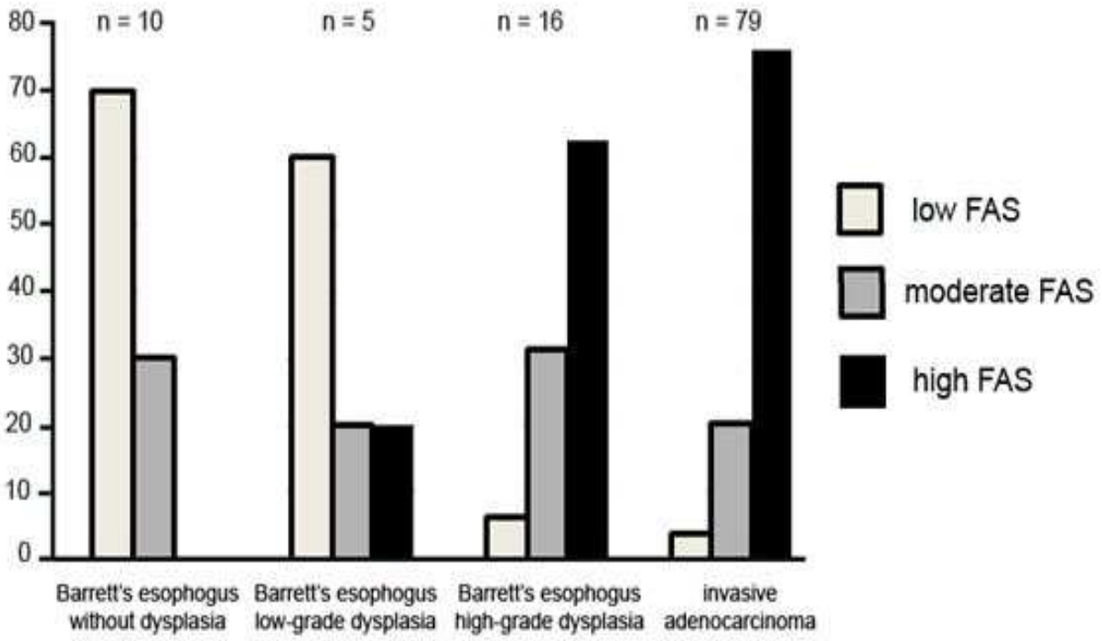


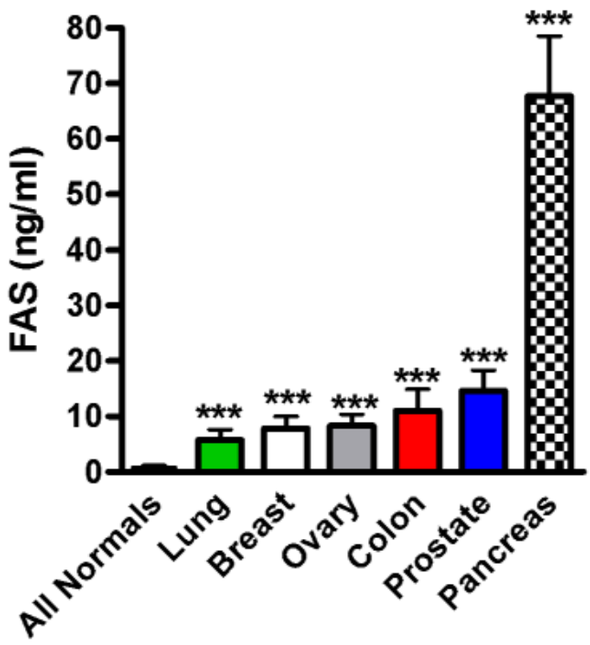
Fig. 1. **FAS expression in SCC and EAC.**
Fatty acid synthase is expressed at high levels in human esophageal squamous cell carcinomas and adenocarcinomas. In addition, FAS is expressed at high levels in Barrett's esophagus with dysplasia.

In addition to being overexpressed in malignant tissues, increased FAS levels can also be detected in the circulation in cancer patients (30, 31), and our group has found that serum FAS levels could potentially be used as tumor marker. Figure2 shows the data of FAS serum in several cancers, where each cancer shows high levels of FAS compared with control. For esophageal cancer, we compared levels FAS in serum from 150 patients with invasive squamous cell carcinoma and 4 with invasive adenocarcinoma to those of 153 normal healthy individuals (Figure 3). The significantly higher levels in cancer patients than control patients suggest that measurements of FAS might be a useful tumor marker.

To explore anti-FAS therapy for esophageal cancer, we first confirmed that FAS expression is also high in xenografts of human esophageal squamous cell cancer cells, with levels that are similar to human tumors. A number of agents are available to inhibit FAS; previous laboratory studies have shown that cancer cell growth can be suppressed by inhibiting the activity of this enzyme FAS with cerulenin (a natural antibiotic), small interfering RNA specific for the FAS gene transcript [99], orlistat, a pancreatic lipase inhibitor developed for obesity treatment [100], or C75, a first-generation synthetic small-molecule developed specifically for inhibiting type 1 mammalian FAS, based on the known mechanism of action of cerulenin[101, 102].

However, efforts to treat xenograft cancers with C75 [103-105] have been hampered by transient, but severe, anorexia and weight loss caused by drug treatment, an effect that could also limit the use of this compound in the clinical setting [106]. C75 is a mimetic of

malonyl-CoA, and in addition to inhibiting FAS, C75 stimulates fatty acid oxidation [most likely by activating carnitine Opalmitoyltransferase-1 (CPT1); ref.[107]]. This, in turn, seems to contribute to the reduction of neuropeptide Y expression in the hypothalamus [97, 106]. Based on these issues, we explored a second-generation drug, C93, which was designed to specifically inhibit FAS without affecting CPT1 activity [108]. Antineoplastic activity, without anorectic effects, can be achieved with this drug by selective pharmacologic inhibition of FAS without stimulation of CPT1, and we demonstrated effective treatment of mice bearing xenografts of the Colo680N squamous cell esophageal cancer cell line using this drug (figure4). Other animal experiments have also found C93 to work well for treatment of cancer xenografts in a variety of other tumor types [98, 109-112], and encouraging results have been seen in cancer chemoprevention experiments [113, 114].



Normals & Cancer	*n*	Average FAS (ng/ml)	Standard Error	p Value (normals)
All Normals	119	0.97	0.18	n.a.
Lung	11	5.76	1.84	p<0.0001
Breast	12	7.85	2.21	p<0.0001
Ovary	13	8.39	1.93	p<0.0001
Colon	10	11.05	3.83	p<0.0001
Prostate	13	14.6	3.68	p<0.0001
Pancreas	20	67.7	10.82	p<0.0001

Fig. 2. **FAS-detect™ IHC serum levels in normal individuals and cancer patients.**

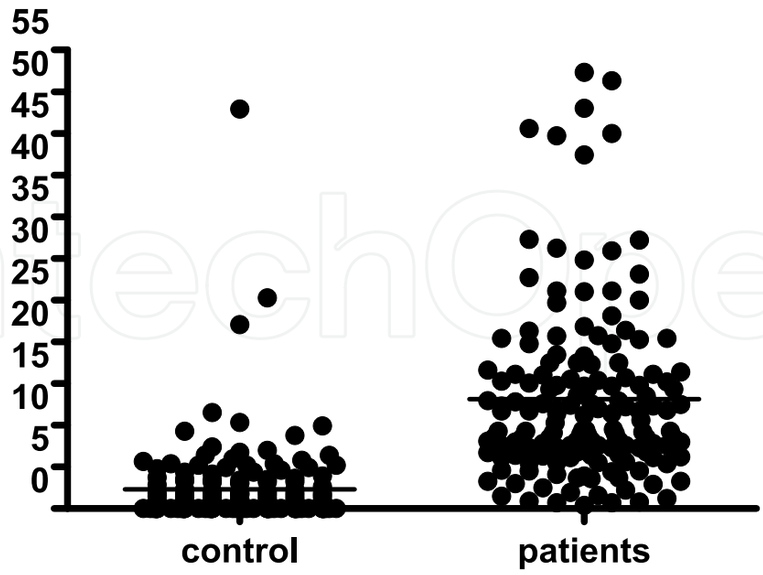


Fig. 3. **Serum FAS level in Esophageal cancer patients are significantly higher than control.**

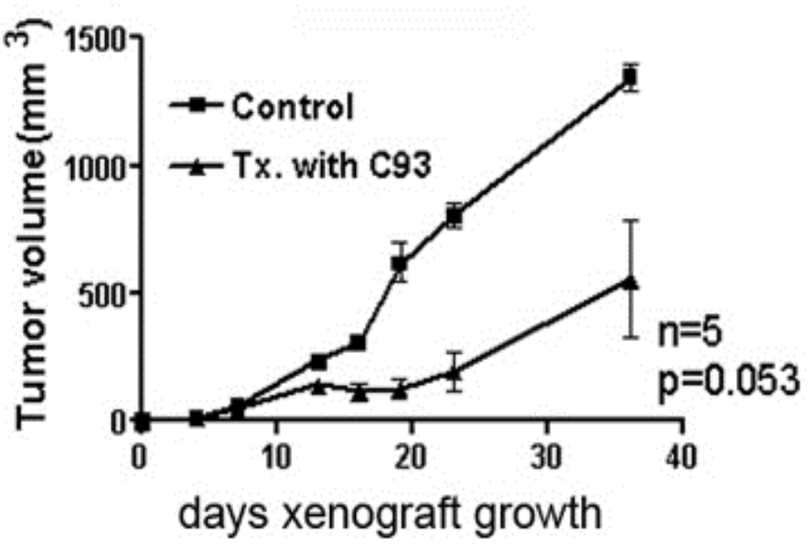


Fig. 4. **Treatment of esophageal cancer xenografts with C93.**

Growth facter
Epidermal growth factor receptor
Her-2/Neu
TKIs
Angiogenesis
Vascular endothelial growth factor
Metabolism target
Metformin
Fatty acid synthase

Table 1. Esophageal cancer: potential targets and markers.

6. Conclusions

In summary, it is well accepted that new targeted drug therapies need to be developed for advanced esophageal cancer due to the poor prognosis of this type of cancer. In this chapter, we have described the current clinical trial molecule targeted agents and metabolic pathways as targets for cancer therapy in esophageal cancer.

Most obviously, high expression levels of EGFR and VGFR in esophageal cancer make antibodies directed against these molecules logical choices for clinical testing. Several phase II studies are now assessing the efficacy of these agents in combination with standard therapy for treatment of esophageal cancer.

Already, the combination of bevacizumab and cetuximab/Panitumumab for patients with metastatic colorectal cancer has shown meaningful clinical benefit, and significant numbers of patients are experiencing prolonged survival with a reasonable quality of life due to these new agents. Within the coming years, several clinical trials will be completed to evaluate these agents for treatment of esophageal cancer. In Head and neck cancer, Cetuximab has also shown efficacy in the treatment. Because of many expressions, we expect this drug for improvement for the treatment of esophageal cancer.

Drugs targeting cellular metabolic pathways are also now attracting great attention for chemotherapy and chemoprevention. In this review, we have described the possibility of metformin for treatment of esophageal cancer based in part on evidence that diabetic patients have increased risks for developing many different types of cancers and clinical data indicating that diabetic patients taking metformin have improved responses to chemotherapy. Finally, fatty acid synthase (FAS) as a novel target for treatment of esophageal cancer was discussed. While clinical data is not yet available for anti-FAS therapy, promising preclinical data warrants attention to this area of investigation.

7. Acknowledgements

Declaration of personal and funding interests: None.

8. References

[1] Eslick, G.D., *Epidemiology of esophageal cancer.* Gastroenterology clinics of North America, 2009. 38(1): p. 17-25, vii.

[2] Herszenyi, L. and Z. Tulassay, *Epidemiology of gastrointestinal and liver tumors.* European review for medical and pharmacological sciences, 2010. 14(4): p. 249-58.

[3] Corley, D.A. and P.A. Buffler, *Oesophageal and gastric cardia adenocarcinomas: analysis of regional variation using the Cancer Incidence in Five Continents database.* International journal of epidemiology, 2001. 30(6): p. 1415-25.

[4] Shimada, H. and T. Ochiai, *Gene therapy for esophageal squamous cell carcinoma.* Frontiers in bioscience : a journal and virtual library, 2008. 13: p. 3364-72.

[5] Herbst, R.S., *Review of epidermal growth factor receptor biology.* International journal of radiation oncology, biology, physics, 2004. 59(2 Suppl): p. 21-6.

[6] Carpenter, G., et al., *Characterization of the binding of 125-I-labeled epidermal growth factor to human fibroblasts.* The Journal of biological chemistry, 1975. 250(11): p. 4297-304.

[7] Rothenberg, M.L., et al., *Randomized phase II trial of the clinical and biological effects of two dose levels of gefitinib in patients with recurrent colorectal adenocarcinoma.* Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 2005. 23(36): p. 9265-74.

[8] Yu, W.W., et al., *Clinicopathological and prognostic significance of EGFR over-expression in esophageal squamous cell carcinoma: a meta-analysis.* Hepato-gastroenterology, 2011. 58(106): p. 426-31.

[9] Cronin, J., et al., *Epidermal growth factor receptor (EGFR) is overexpressed in high-grade dysplasia and adenocarcinoma of the esophagus and may represent a biomarker of histological progression in Barrett's esophagus (BE).* The American journal of gastroenterology, 2011. 106(1): p. 46-56.

[10] Friess, H., et al., *Concomitant analysis of the epidermal growth factor receptor family in esophageal cancer: overexpression of epidermal growth factor receptor mRNA but not of c-erbB-2 and c-erbB-3.* World journal of surgery, 1999. 23(10): p. 1010-8.

[11] Laskin, J.J. and A.B. Sandler, *Epidermal growth factor receptor: a promising target in solid tumours.* Cancer treatment reviews, 2004. 30(1): p. 1-17.

[12] Scagliotti, G.V., et al., *The biology of epidermal growth factor receptor in lung cancer.* Clinical cancer research : an official journal of the American Association for Cancer Research, 2004. 10(12 Pt 2): p. 4227s-4232s.

[13] Ang, K.K., et al., *Impact of epidermal growth factor receptor expression on survival and pattern of relapse in patients with advanced head and neck carcinoma.* Cancer research, 2002. 62(24): p. 7350-6.

[14] Gibault, L., et al., *Diffuse EGFR staining is associated with reduced overall survival in locally advanced oesophageal squamous cell cancer.* British journal of cancer, 2005. 93(1): p. 107-15.

[15] Hirsch, F.R., et al., *Epidermal growth factor receptor in non-small-cell lung carcinomas: correlation between gene copy number and protein expression and impact on prognosis.* Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 2003. 21(20): p. 3798-807.

[16] Chung, C.H., et al., *Increased epidermal growth factor receptor gene copy number is associated with poor prognosis in head and neck squamous cell carcinomas.* Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 2006. 24(25): p. 4170-6.

[17] Baselga, J., *Monoclonal antibodies directed at growth factor receptors.* Annals of oncology : official journal of the European Society for Medical Oncology / ESMO, 2000. 11 Suppl 3: p. 187-90.

[18] Cunningham, D., et al., *Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer.* The New England journal of medicine, 2004. 351(4): p. 337-45.

[19] Saltz, L.B., et al., *Phase II trial of cetuximab in patients with refractory colorectal cancer that expresses the epidermal growth factor receptor.* Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 2004. 22(7): p. 1201-8.

[20] Cohen, R.B., *Epidermal growth factor receptor as a therapeutic target in colorectal cancer.* Clinical colorectal cancer, 2003. 2(4): p. 246-51.

[21] Joy, A.A. and C.A. Butts, *Extending outcomes: epidermal growth factor receptor-targeted monoclonal antibodies in non-small-cell lung cancer.* Clinical lung cancer, 2009. 10 Suppl 1: p. S24-9.

[22] Chung, C.H., et al., *Detection of tumor epidermal growth factor receptor pathway dependence by serum mass spectrometry in cancer patients.* Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology, 2010. 19(2): p. 358-65.

[23] Ibrahim, E.M., et al., *Cetuximab-based Therapy is Effective in Chemotherapy-naive Patients with Advanced and Metastatic Non-small-cell Lung Cancer: A Meta-analysis of Randomized Controlled Trials.* Lung, 2011. 189(3): p. 193-8.

[24] Stinchcombe, T.E. and M.A. Socinski, *Targeted therapies: Biomarkers in NSCLC for selecting cetuximab therapy.* Nature reviews. Clinical oncology, 2010. 7(8): p. 426-8.

[25] Ademuyiwa, F.O. and N. Hanna, *Cetuximab in non-small cell lung cancer.* Expert opinion on biological therapy, 2008. 8(1): p. 107-13.

[26] Bonner, J.A., et al., *Epidermal growth factor receptor as a therapeutic target in head and neck cancer.* Seminars in radiation oncology, 2002. 12(3 Suppl 2): p. 11-20.

[27] Licitra, L., et al., *Role of EGFR family receptors in proliferation of squamous carcinoma cells induced by wound healing fluids of head and neck cancer patients.* Annals of oncology : official journal of the European Society for Medical Oncology / ESMO, 2011.

[28] Smith, D., C. Bosacki, and Y. Merrouche, *[Use of anti-EGFR antibodies (cetuximab and panitumumab) in the treatment of metastatic colorectal cancer in KRAS wild type patients].* Bulletin du cancer, 2009. 96 Suppl: p. S31-40.

[29] Russo, A., et al., *The long and winding road to useful predictive factors for anti-EGFR therapy in metastatic colorectal carcinoma: the KRAS/BRAF pathway.* Oncology, 2009. 77 Suppl 1: p. 57-68.

[30] Lopez-Gomez, M., et al., *Different patterns of toxicity after sequential administration of two anti-EGFR monoclonal antibodies.* Clinical & translational oncology : official

publication of the Federation of Spanish Oncology Societies and of the National Cancer Institute of Mexico, 2010. 12(11): p. 775-7.

[31] Rother, M., *Impact of a pre-emptive skin treatment regimen on skin toxicities of anti-epidermal growth factor receptor monoclonal antibodies: more questions than answers.* Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 2010. 28(27): p. e474; author reply e475-6.

[32] Zhang, W., M. Gordon, and H.J. Lenz, *Novel approaches to treatment of advanced colorectal cancer with anti-EGFR monoclonal antibodies.* Annals of medicine, 2006. 38(8): p. 545-51.

[33] Benvenuti, S., et al., *Oncogenic activation of the RAS/RAF signaling pathway impairs the response of metastatic colorectal cancers to anti-epidermal growth factor receptor antibody therapies.* Cancer research, 2007. 67(6): p. 2643-8.

[34] Karapetis, C.S., et al., *K-ras mutations and benefit from cetuximab in advanced colorectal cancer.* The New England journal of medicine, 2008. 359(17): p. 1757-65.

[35] Amado, R.G., et al., *Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer.* Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 2008. 26(10): p. 1626-34.

[36] Markman, B., et al., *EGFR and KRAS in colorectal cancer.* Advances in clinical chemistry, 2010. 51: p. 71-119.

[37] De Vita, F., et al., *A multicenter phase II study of induction chemotherapy with FOLFOX-4 and cetuximab followed by radiation and cetuximab in locally advanced oesophageal cancer.* British journal of cancer, 2011. 104(3): p. 427-32.

[38] Gold, P.J., et al., *Cetuximab as second-line therapy in patients with metastatic esophageal adenocarcinoma: a phase II Southwest Oncology Group Study (S0415).* Journal of thoracic oncology : official publication of the International Association for the Study of Lung Cancer, 2010. 5(9): p. 1472-6.

[39] Lorenzen, S., et al., *Cetuximab plus cisplatin-5-fluorouracil versus cisplatin-5-fluorouracil alone in first-line metastatic squamous cell carcinoma of the esophagus: a randomized phase II study of the Arbeitsgemeinschaft Internistische Onkologie.* Annals of oncology : official journal of the European Society for Medical Oncology / ESMO, 2009. 20(10): p. 1667-73.

[40] Janmaat, M.L., et al., *Predictive factors for outcome in a phase II study of gefitinib in second-line treatment of advanced esophageal cancer patients.* Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 2006. 24(10): p. 1612-9.

[41] Zhao, Y., et al., *Preclinical evaluation of a potent novel DNA-dependent protein kinase inhibitor NU7441.* Cancer research, 2006. 66(10): p. 5354-62.

[42] Mok, T.S., et al., *Randomized, placebo-controlled, phase II study of sequential erlotinib and chemotherapy as first-line treatment for advanced non-small-cell lung cancer.* Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 2009. 27(30): p. 5080-7.

[43] Rodriguez, C.P., et al., *A phase II study of perioperative concurrent chemotherapy, gefitinib, and hyperfractionated radiation followed by maintenance gefitinib in locoregionally advanced esophagus and gastroesophageal junction cancer.* Journal of thoracic oncology :

official publication of the International Association for the Study of Lung Cancer, 2010. 5(2): p. 229-35.

[44] Altiok, S., et al., *A novel pharmacodynamic approach to assess and predict tumor response to the epidermal growth factor receptor inhibitor gefitinib in patients with esophageal cancer.* International journal of oncology, 2010. 36(1): p. 19-27.

[45] Ilson, D.H., et al., *A phase 2 trial of erlotinib in patients with previously treated squamous cell and adenocarcinoma of the esophagus.* Cancer, 2011. 117(7): p. 1409-14.

[46] Burris, H.A., 3rd, *Dual kinase inhibition in the treatment of breast cancer: initial experience with the EGFR/ErbB-2 inhibitor lapatinib.* The oncologist, 2004. 9 Suppl 3: p. 10-5.

[47] Higa, G.M. and J. Abraham, *Lapatinib in the treatment of breast cancer.* Expert review of anticancer therapy, 2007. 7(9): p. 1183-92.

[48] Bouchalova, K., et al., *Triple negative breast cancer--current status and prospective targeted treatment based on HER1 (EGFR), TOP2A and C-MYC gene assessment.* Biomedical papers of the Medical Faculty of the University Palacky, Olomouc, Czechoslovakia, 2009. 153(1): p. 13-7.

[49] Hurvitz, S.A. and R.S. Finn, *What's positive about 'triple-negative' breast cancer?* Future oncology, 2009. 5(7): p. 1015-25.

[50] Hector, A., et al., *The Axl receptor tyrosine kinase is an adverse prognostic factor and a therapeutic target in esophageal adenocarcinoma.* Cancer biology & therapy, 2010. 10(10): p. 1009-18.

[51] Hung, M.C. and Y.K. Lau, *Basic science of HER-2/neu: a review.* Seminars in oncology, 1999. 26(4 Suppl 12): p. 51-9.

[52] Coussens, L., et al., *Tyrosine kinase receptor with extensive homology to EGF receptor shares chromosomal location with neu oncogene.* Science, 1985. 230(4730): p. 1132-9.

[53] Lee, K.F., et al., *Requirement for neuregulin receptor erbB2 in neural and cardiac development.* Nature, 1995. 378(6555): p. 394-8.

[54] Crone, S.A., et al., *ErbB2 is essential in the prevention of dilated cardiomyopathy.* Nature medicine, 2002. 8(5): p. 459-65.

[55] Olayioye, M.A., *Update on HER-2 as a target for cancer therapy: intracellular signaling pathways of ErbB2/HER-2 and family members.* Breast cancer research : BCR, 2001. 3(6): p. 385-9.

[56] Jung, S.Y., et al., *Worse prognosis of metaplastic breast cancer patients than other patients with triple-negative breast cancer.* Breast cancer research and treatment, 2010. 120(3): p. 627-37.

[57] Kim, K.C., et al., *Evaluation of HER2 Protein Expression in Gastric Carcinomas: Comparative Analysis of 1414 Cases of Whole-Tissue Sections and 595 Cases of Tissue Microarrays.* Annals of surgical oncology, 2011.

[58] Lin, C.K., et al., *Assessing the Impact of Polysomy-17 on HER2 Status and the Correlations of HER2 Status With Prognostic Variables (ER, PR, p53, Ki-67) in Epithelial Ovarian Cancer: A Tissue Microarray Study Using Immunohistochemistry and Fluorescent In Situ Hybridization.* International journal of gynecological pathology : official journal of the International Society of Gynecological Pathologists, 2011. 30(4): p. 372-379.

[59] Stoecklein, N.H., et al., *Copy number of chromosome 17 but not HER2 amplification predicts clinical outcome of patients with pancreatic ductal adenocarcinoma.* Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 2004. 22(23): p. 4737-45.

[60] Yamanaka, Y., et al., *Overexpression of HER2/neu oncogene in human pancreatic carcinoma.* Human pathology, 1993. 24(10): p. 1127-34.

[61] Yentz, S. and T.D. Wang, *Molecular imaging for guiding oncologic prognosis and therapy in esophageal adenocarcinoma.* Hospital practice, 2011. 39(2): p. 97-106.

[62] Safran, H., et al., *Phase I/II study of trastuzumab, paclitaxel, cisplatin and radiation for locally advanced, HER2 overexpressing, esophageal adenocarcinoma.* International journal of radiation oncology, biology, physics, 2007. 67(2): p. 405-9.

[63] Szentirmay, Z., *[Effect of learning about the human genome on the development of pathology].* Orvosi hetilap, 2003. 144(51): p. 2499-508.

[64] Wei, Q., et al., *EGFR, HER2 and HER3 expression in esophageal primary tumours and corresponding metastases.* International journal of oncology, 2007. 31(3): p. 493-9.

[65] Zhan, N., et al., *Analysis of HER2 gene amplification and protein expression in esophageal squamous cell carcinoma.* Medical oncology, 2011.

[66] Baselga, J., et al., *Phase II study of weekly intravenous recombinant humanized anti-p185HER2 monoclonal antibody in patients with HER2/neu-overexpressing metastatic breast cancer.* Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 1996. 14(3): p. 737-44.

[67] Slamon, D.J., et al., *Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2.* The New England journal of medicine, 2001. 344(11): p. 783-92.

[68] Le, X.F., F. Pruefer, and R.C. Bast, Jr., *HER2-targeting antibodies modulate the cyclin-dependent kinase inhibitor p27Kip1 via multiple signaling pathways.* Cell cycle, 2005. 4(1): p. 87-95.

[69] Bang, Y.J., et al., *Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial.* Lancet, 2010. 376(9742): p. 687-97.

[70] Senger, D.R., et al., *Tumor cells secrete a vascular permeability factor that promotes accumulation of ascites fluid.* Science, 1983. 219(4587): p. 983-5.

[71] Kulke, M.H., et al., *Prognostic significance of vascular endothelial growth factor and cyclooxygenase 2 expression in patients receiving preoperative chemoradiation for esophageal cancer.* The Journal of thoracic and cardiovascular surgery, 2004. 127(6): p. 1579-86.

[72] Coughlin, S.S., et al., *Diabetes mellitus as a predictor of cancer mortality in a large cohort of US adults.* American journal of epidemiology, 2004. 159(12): p. 1160-7.

[73] Levine, W., et al., *Post-load plasma glucose and cancer mortality in middle-aged men and women. 12-year follow-up findings of the Chicago Heart Association Detection Project in Industry.* American journal of epidemiology, 1990. 131(2): p. 254-62.

[74] Saydah, S.H., et al., *Abnormal glucose tolerance and the risk of cancer death in the United States.* American journal of epidemiology, 2003. 157(12): p. 1092-100.

[75] Steevens, J., et al., *A prospective cohort study on overweight, smoking, alcohol consumption, and risk of Barrett's esophagus.* Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology, 2011. 20(2): p. 345-58.

[76] Bechade, D., et al., *[Review of the association between obesity and gastroesophageal reflux and its complications].* Gastroenterologie clinique et biologique, 2009. 33(3): p. 155-66.

[77] El-Serag, H., *The association between obesity and GERD: a review of the epidemiological evidence.* Digestive diseases and sciences, 2008. 53(9): p. 2307-12.

[78] Lee, M.S., et al., *Type 2 diabetes increases and metformin reduces total, colorectal, liver and pancreatic cancer incidences in Taiwanese: a representative population prospective cohort study of 800,000 individuals.* BMC cancer, 2011. 11: p. 20.

[79] Guh, D.P., et al., *The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis.* BMC public health, 2009. 9: p. 88.

[80] Cheng, K.K., et al., *A case-control study of oesophageal adenocarcinoma in women: a preventable disease.* British journal of cancer, 2000. 83(1): p. 127-32.

[81] Rubenstein, J.H., et al., *Relationship between diabetes mellitus and adenocarcinoma of the oesophagus and gastric cardia.* Alimentary pharmacology & therapeutics, 2005. 22(3): p. 267-71.

[82] Neale, R.E., et al., *Does type 2 diabetes influence the risk of oesophageal adenocarcinoma?* British journal of cancer, 2009. 100(5): p. 795-8.

[83] Yang, Y.X., *Do diabetes drugs modify the risk of pancreatic cancer?* Gastroenterology, 2009. 137(2): p. 412-5.

[84] Yang, Y.X., S. Hennessy, and J.D. Lewis, *Insulin therapy and colorectal cancer risk among type 2 diabetes mellitus patients.* Gastroenterology, 2004. 127(4): p. 1044-50.

[85] Chong, C.R. and B.A. Chabner, *Mysterious metformin.* The oncologist, 2009. 14(12): p. 1178-81.

[86] Nathan, D.M., et al., *Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes.* Diabetes care, 2009. 32(1): p. 193-203.

[87] Evans, J.M., et al., *Metformin and reduced risk of cancer in diabetic patients.* BMJ, 2005. 330(7503): p. 1304-5.

[88] Bowker, S.L., et al., *Increased cancer-related mortality for patients with type 2 diabetes who use sulfonylureas or insulin.* Diabetes care, 2006. 29(2): p. 254-8.

[89] Zhou, K., et al., *Common variants near ATM are associated with glycemic response to metformin in type 2 diabetes.* Nature genetics, 2011. 43(2): p. 117-20.

[90] Lizcano, J.M., et al., *LKB1 is a master kinase that activates 13 kinases of the AMPK subfamily, including MARK/PAR-1.* The EMBO journal, 2004. 23(4): p. 833-43.

[91] Jiralerspong, S., et al., *Metformin and pathologic complete responses to neoadjuvant chemotherapy in diabetic patients with breast cancer.* Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 2009. 27(20): p. 3297-302.

[92] Hirsch, H.A., et al., *Metformin selectively targets cancer stem cells, and acts together with chemotherapy to block tumor growth and prolong remission.* Cancer research, 2009. 69(19): p. 7507-11.

[93] 93. Kuhajda, F.P., *Fatty-acid synthase and human cancer: new perspectives on its role in tumor biology.* Nutrition, 2000. 16(3): p. 202-8.

[94] Nemoto, T., et al., *Overexpression of fatty acid synthase in oesophageal squamous cell dysplasia and carcinoma.* Pathobiology : journal of immunopathology, molecular and cellular biology, 2001. 69(6): p. 297-303.

[95] Weiss, L., et al., *Fatty-acid biosynthesis in man, a pathway of minor importance. Purification, optimal assay conditions, and organ distribution of fatty-acid synthase.* Biological chemistry Hoppe-Seyler, 1986. 367(9): p. 905-12.

[96] Ishimura, N., et al., *Fatty Acid Synthase Expression in Barrett's Esophagus: Implications for Carcinogenesis.* Journal of clinical gastroenterology, 2011.

[97] Crispino, P., et al., *Evaluation of fatty acid synthase expression in oesophageal mucosa of patients with oesophagitis, Barrett's oesophagus and adenocarcinoma.* Journal of cancer research and clinical oncology, 2009. 135(11): p. 1533-41.

[98] Orita, H., et al., *High levels of fatty acid synthase expression in esophageal cancers represent a potential target for therapy.* Cancer biology & therapy, 2010. 10(6): p. 549-54.

[99] De Schrijver, E., et al., *RNA interference-mediated silencing of the fatty acid synthase gene attenuates growth and induces morphological changes and apoptosis of LNCaP prostate cancer cells.* Cancer research, 2003. 63(13): p. 3799-804.

[100] Kridel, S.J., et al., *Orlistat is a novel inhibitor of fatty acid synthase with antitumor activity.* Cancer research, 2004. 64(6): p. 2070-5.

[101] Kuhajda, F.P., et al., *Fatty acid synthesis: a potential selective target for antineoplastic therapy.* Proceedings of the National Academy of Sciences of the United States of America, 1994. 91(14): p. 6379-83.

[102] Kuhajda, F.P., et al., *Synthesis and antitumor activity of an inhibitor of fatty acid synthase.* Proceedings of the National Academy of Sciences of the United States of America, 2000. 97(7): p. 3450-4.

[103] Gabrielson, E.W., et al., *Increased fatty acid synthase is a therapeutic target in mesothelioma.* Clinical cancer research : an official journal of the American Association for Cancer Research, 2001. 7(1): p. 153-7.

[104] Pizer, E.S., et al., *Increased fatty acid synthase as a therapeutic target in androgen-independent prostate cancer progression.* The Prostate, 2001. 47(2): p. 102-10.

[105] Wang, H.Q., et al., *Positive feedback regulation between AKT activation and fatty acid synthase expression in ovarian carcinoma cells.* Oncogene, 2005. 24(22): p. 3574-82.

[106] Loftus, T.M., et al., *Reduced food intake and body weight in mice treated with fatty acid synthase inhibitors.* Science, 2000. 288(5475): p. 2379-81.

[107] Thupari, J.N., et al., *C75 increases peripheral energy utilization and fatty acid oxidation in diet-induced obesity.* Proceedings of the National Academy of Sciences of the United States of America, 2002. 99(14): p. 9498-502.

[108] McFadden, J.M., et al., *Application of a flexible synthesis of (5R)-thiolactomycin to develop new inhibitors of type I fatty acid synthase.* Journal of medicinal chemistry, 2005. 48(4): p. 946-61.

[109] Orita, H., et al., *Selective inhibition of fatty acid synthase for lung cancer treatment.* Clinical cancer research : an official journal of the American Association for Cancer Research, 2007. 13(23): p. 7139-45.

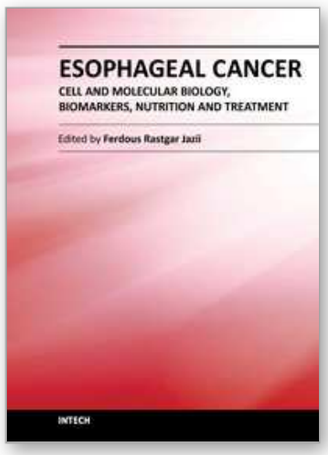
[110] Ueda, S.M., et al., *Trophoblastic neoplasms express fatty acid synthase, which may be a therapeutic target via its inhibitor C93.* The American journal of pathology, 2009. 175(6): p. 2618-24.

[111] Ueda, S.M., et al., *Expression of Fatty Acid Synthase Depends on NAC1 and Is Associated with Recurrent Ovarian Serous Carcinomas.* Journal of oncology, 2010. 2010: p. 285191.

[112] Zhou, W., et al., *Fatty acid synthase inhibition activates AMP-activated protein kinase in SKOV3 human ovarian cancer cells.* Cancer research, 2007. 67(7): p. 2964-71.

[113] Orita, H., et al., *Inhibiting fatty acid synthase for chemoprevention of chemically induced lung tumors.* Clinical cancer research : an official journal of the American Association for Cancer Research, 2008. 14(8): p. 2458-64.

[114] Alli, P.M., et al., *Fatty acid synthase inhibitors are chemopreventive for mammary cancer in neu-N transgenic mice.* Oncogene, 2005. 24(1): p. 39-46.



Esophageal Cancer - Cell and Molecular Biology, Biomarkers, Nutrition and Treatment

Edited by Prof. Ferdous Rastgar Jazii

ISBN 978-953-51-0223-6
Hard cover, 244 pages
Publisher InTech
Published online 07, March, 2012
Published in print edition March, 2012

Esophageal Cancer illustrates recent achievements and investigations in the esophageal tumorigenesis from different perspectives. Readers find mechanisms involved in esophageal tumorigenesis, cellular, molecular, genetic, epigenetics, and proteomics, their relevance as the novel biomarkers and application in esophageal cancer diagnosis and therapy. The book covers detailed effect of nutritional factors in addition to ethanol metabolic pathway in the inhibition of retinoic acid metabolism and supply. Diagnosis, classification, and treatment of esophageal cancer, application of both surgical and non surgical methods as well as follow up of the disease are described in detail. Moreover readers are endowed with especial features of esophageal cancer such as multiple early stage malignant melanoma and pulmonary edema induced by esophagectomy, the two features that received less attention elsewhere in literature.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Hajime Orita, Malcolm Brock and Koichi Sato (2012). Emerging Therapies for Esophageal Cancer, Esophageal Cancer - Cell and Molecular Biology, Biomarkers, Nutrition and Treatment, Prof. Ferdous Rastgar Jazii (Ed.), ISBN: 978-953-51-0223-6, InTech, Available from: http://www.intechopen.com/books/esophageal-cancer-cell-and-molecular-biology-biomarkers-nutrition-and-treatment/emerging-therapies-for-esophageal-cancer

INTECH
open science | open minds

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

IntechOpen