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# Biomarkers, Stem Cells and Esophageal Cancer

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## 1. Introduction

There are two main forms of esophagus cancer with different malignant behaviors: epidermal or squamous carcinoma (ESCC) and esophagus adenocarcinoma (EA). ESCC is associated with ethanol and tobacco consumption (tobacco-specific-N-nitroso compounds). ESCC is among the more aggressive cancers known. The high mortality rate associated with this type of cancer is directly related to a late diagnosis. Thus there is an important challenge to identify biomarkers for early diagnosis (Shimada et al., 2003; Sobin & Fleming, 1997).

EA starts from a metaplasia mucosa-dysplasia-carcinoma sequence in the distal esophagus (Barrett's esophagus (BE)), as a result of local injury and is associated with risk of malignant transformation. Cellular proliferation takes place through the subsequent phases of the cell cycle. During the cell cycle, there are different check points and, the transition from G1 to S phase is the most studied in neoplastic progression of Barrett's cells and alterations in growth factor expression. Its receptors and/or the signal transduction pathways have been found at various stages during the progression of metaplasia to EA (Lao-Sirieix et al., 2007; Lord et al., 2000). BE is clinically important because the risk of progressing to adenocarcinoma under the chronically damaging effect of gastrointestinal reflux. EA of the upper esophagus is rare and in some cases develops from areas of gastric heterotopias. It has been hypothesized that intestinal metaplasia could have a change in their differentiation pattern. Indeed, a clonal selection model suggests that malignant transformation occurs by multiple allelic alterations (Nowell, 1976; Souza et al., 2008).

The incidence of EA has increased in the last 40 years. However, the biology of both, the normal esophageal epithelium and the pathogenesis involved in the development of esophageal cancer are not well understood. Epithelial changes are due to stimulation of esophageal stem cells of the epithelium. These changes in the activity of the esophagus stem cells and the up- or down-regulation of stem cell markers appear to be related in the pathogenesis of esophageal cancer and final clinical outcome. Over the last 5 years, important progress has been made in the identification and understanding of adult gastrointestinal stem cells. However, esophageal stem cells are not well characterized. Isolation and characterization of adult esophageal stem cells and the factors that contribute to the development of dysplasia and malignancy is a very important issue for the development of efficient therapies for esophageal cancer (Adams and Strasser, 2008; Croagh

et al., 2008; Hormi-Carver and Souza, 2009). The clonal selection theory was thought to be responsible for the development of gastrointestinal cancers, based on the evidence that some cells acquire genetic alterations giving them the capacity of self-renewal (Adams and Strasser, 2008). Recently, the cancer stem cell (CSC) theory has gained more attention based on the idea that some cancers are initiated by stem cells with genetic alterations. Cellular and tissue regeneration is based on the characteristics of self-renewal and multipotency of stem cells. In recent years, progress in stem cell identification and characterization indicate their potential therapeutic applications in regenerative medicine for the treatment of several pathologies. The different types of stem cells, embryonic, induced pluripotent and adult stem cells are emerging as a potential approach to treat gastrointestinal disorders.

## 2. Biomarkers or bio-indicators

The so called tumor markers and biological markers are usually used in place of each other. Initially, tumor markers were developed and used to detect some mucin antigens on the cancer cell surface and/or in the serum of cancer patients. Those tumor markers on the cell surface that form glyco-conjugates are involved in adhesion, motility and metastasis. The tumor markers can induce the immune response early during malignant transformation, and later are shed by cancer cells into blood vessels and detected in serum or plasma. The ideal tumor marker have to be specific for malignant cells, detectable early in the carcinogenesis process, measurable by simple invasive methods and the concentrations measured have to be proportional to the stage of malignancy and/or a pharmacological response to therapeutic intervention. There are different tumor markers, each indicative of a particular disease process and used in oncology to detect the presence of a cancer. Tumor markers can be produced by the tumor cells or by the non-tumor cells as a response to the presence of a disease. This was used for identification, evaluation and follows up of treatment, either for patients based or population based and even experimental condition. Brief descriptions for it were focused on these tumor markers in different cancer types. The carcinoembryonic antigen CEA, is a glycoprotein involved in cell adhesion that was studied in lung carcinoma (Vegh et al., 2002) and colorectal carcinoma (Vegh et al., 2007). Cancer antigen 125 (CA 125) was used principally for screening ovarian cancer (Frederick et al., 2011). CA 19.9, also called carbohydrate antigen 19-9 was detected in colorectal carcinoma (Morales-Gutierrez et al., 1999; Vegh et al., 2003). Alpha fetoprotein (AFP) levels were increased in hepatocellular carcinoma and esophagus carcinoma (Bellet et al., 1984). Beta human chorionic gonadotropin ( $\beta$ HCG) was evaluated in different diseases (Burg-Kurland et al., 1989). Carbohydrate antigen 15.3 (CA 15.3) was mostly studied in breast carcinoma (Bearz et al., 2007). Some epidemiologic studies observed that the incidence for EA in all races had variations according to this histology, age and gender. There is a striking male predominance in esophageal cancer. Sex hormones have been suggested as a contributing factor and these are influenced by histology, age and race. The highest sex ratios were seen in esophagus EA in the age group between 50-59 years old, rendering plausibility to the hypothesis that female sex hormone exposure may play a protective role in the development of this type of cancer (Nordenstedt et al., 2011).

Nowadays, biomarkers or bio-indicators in cell biology are molecules that allow the detection and isolation of a particular cell type. In genetics, a biomarker is a DNA sequence that causes or is associated with the development of diseases. Biomarkers are used to

indicate the variation in the expression of a characteristic protein that correlates with the risk of development of pathology. Currently, most biomarkers used in clinic are proteins, while based on genetics they might be DNA or RNA and they could also be subject of determination or application in clinic, specially in case of viral infected or DNA or RNA which are shed from individual tumor tissue stream. The expression of several biomarkers in plasma and tissue from patients with esophagus cancer were analyzed, and looked for the biomarkers whose over-expression could be associated with a different behavior in esophagus cancer and could have potential prognostic implications.

In this chapter our aim was to discuss each specific biomarker in separate sections in the context of esophageal cancer, as some of these markers are also important in the development and evolution of other types of tumors.

## 2.1 Metalloproteinase

The extracellular matrix (ECM) is the extracellular part of a tissue which provides support to cells and is known as connective tissue (Bosman and Stamenkovic, 2003). ECM includes the interstitial matrix and the basement membrane. EMC is composed of a variety of proteins and glycoaminoglicans. Numerous families of enzymes (proteinases) are responsible for the degradation of ECM. The family of enzymes called matrix metalloproteinases (MMPs) are the major enzymes implicated in extracellular degradation and are essential for embryonic development, morphogenesis, remodeling and tissue repair. MMPs are classified into five classes: collagenases (MMP-1,-8 and -13), gelatinases (MMP-2 and -9), stromelysins (MMP-3 and -10), membrane type matrilysins (MMP-7 and -26) and others. The MMPs are zinc-dependent endo-peptidases and are inhibited by specific endogenous inhibitors, the tissue inhibitor of metalloproteinases (TIMP). This MMPs family currently includes more than 26 members. Proteases not only have cell-matrix interaction, but also can control the progression of angiogenesis by activating growth factors such as hepatocyte growth factor (HGF), basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF) and can influence cellular behavior. MMPs can act also as an inhibitor of angiogenesis. The data indicate that proteases can acts either as positive or negative regulators of angiogenesis (Brooks et al., 1998). MMP-1 is an interstitial collagenase secreted from fibroblasts, macrophages and keratocytes. MMP-1 is related to cancer aggressiveness and its expression is associated with a multistep carcinogenesis from BE to EA according to the clonal selection model (Etoh et al., 2000; Grimm et al., 2010). MMP-7 (matrilysin) is the smallest molecule of the MMPs, whose function is to degrade elastin, proteoglycans, fibronectin and type IV collagen. It has been found that MMP-7 was over-expressed in a variety of epithelial and mesenchymal tumors such as esophagus, colon, liver, renal, and pancreas. Increased circulating levels of MMP-7 proteins were correlated with the presence of metastatic disease and poor patient survival in colorectal and renal cell cancer (Maurel et al., 2007; Szarvas et al., 2010; Yamamoto et al., 1999; Yamashita et al., 2000). Some authors concluded that the autoantibody levels of MMP-7 in serum may be a good biomarker for ESCC (J.H. Zhou et al., 2011). Some pharmacologic studies designed various MMP inhibitors with poor effect probably due to their high toxicity as has been demonstrated in clinical trials.

TIMPs (tissue inhibitor of metalloproteinases) comprise a family of four protease inhibitors: TIMP-1 (chromosome Xp11.3-p11.23); TIMP-2 (chromosome 17q25); TIMP-3 (chromosome

22q12.3); TIMP4 (chromosome 3q25). The first TIMP was described in 1975 as a protein which was able to inhibit collagenase activity (Bauer et al., 1975; Bosman and Stamenkovic, 2003). TIMPs and MMPs are found in all fluids, such as serum, plasma, urine, etc. All MMPs are inhibited by TIMPs once they are activated. The balance between MMPs and TIMPs plays a necessary role in maintaining the integrity of healthy tissue. An alteration of this balance is observed in different diseases. In cancer and rheumatoid arthritis, the imbalance is generally in favor of MMPs. By contrast to inhibition of MMPs by TIMPs, some studies founded that TIMP-2 was implicated in the activation of pro-MMP-2. This mechanism stimulates cell migration and progression to tumor metastasis and invasion (Yoshizuki et al., 2001). TIMPs are co-expressed with MMPs which depend on endogenously expressed growth factors and cytokines (Gomez et al., 1997).

The balance between MMPs and TIMPs is variable in both, in physiological processes such as growth and development, and in some diseases such as cancer. In esophagus cancer, we studied MMP-1 concentration in tumor and in non-tumor areas from the same patient with EA and observed a higher concentration in tumor areas (Vegh et al., 2007). Moreover, MMP-1 was associated with poor clinical outcome in esophageal cancer in different studies (Etoh et al., 2000; Murray et al., 1998; Yamashita et al., 2001). We found similar results in the concentration of MMP-1 in tumor vs. non-tumor areas in patients who had ESCC, but without being associated with the clinicopathological outcome (Vegh et al., 2007). On the other hand, we have observed that TIMP-1 expression in esophagus cancer showed higher values in tumor areas (Vegh et al., 2007). Interestingly, the same patients with lymph node negative showed higher values on TIMP-1 expression, whereas patients with more than three positive lymph nodes had lower values. This profile could indicate an inhibitory function for TIMP-1 on tumor growth and its possible dissemination. Numerous researchers considered that TIMP-1 has mitogenic activity on different cell types, whereas its over-expression reduced tumor growth in gastric carcinoma (Mimori et al., 1997). Furthermore, studies focusing on nitric oxide (NO) showed enhanced expression of MMP-1,-3,-7 and TIMP-1 in the progression from non-dysplastic BE to adenocarcinoma. This could indicate that NO play a role in Barrett's carcinogenesis through deregulating of MMP and TIMP expression to enhance invasive potential in dysplastic cells (Clemons et al., 2010). MMP-7 was cloned from ESCC tissues and higher levels were observed in serum in patients with ESCC than in their matched-control samples, therefore it was considered that MMP-7 may be a good diagnostic biomarker for ESCC (J.H. Zhou et al., 2011).

## 2.2 Polymorphisms and mutations

It has been well established that cancer is a genetic disease and carcinogenesis takes place in somatic mutations of the oncogenes or tumor suppressor genes. There have been several studies showing that BE and EA can occur within families indicating an inherent genetic risk (Eng et al., 1993; Romero et al., 1997). A pivotal role corresponds to phosphatidylinositol 3-kinase (PIK3CA) signaling pathway. In vitro ESCC proliferation was reduced by a PIK3CA inhibitor. This inhibition has more effects on the cells that contain a PIK3CA gene mutation than those without such mutation (Mori et al., 2008). It has also been speculated that some polymorphisms affecting the inflammatory response might be important in esophageal carcinoma. Such approaches may allow the identification of subsets of individuals within a population who are predisposed to EA. Accumulation of genetic



alterations follows the dysplasia-adenocarcinoma sequence in the esophagus and identifies the patients with poor prognosis (Wu et al., 1998). The human genome receives exogenous and endogenous attacks that could promote genetic mutations, chromosomal rearrangements and finally development of cancer. Cells have an anti-DNA-damaging system to blockade both metabolic and external sources of DNA damaging agents. Activation of cell cycle checkpoints and DNA repair system are complex processes which help cellular responses to DNA damage. These checkpoints generally stop cell-cycle progression at the G1, S, and G2 phases. Gamma-radiation can induce single and double strand breaks. Some chemical carcinogenetic compounds, such as benzo(a) pyrene-diol-epoxide a tobacco procarcinogen benzo(a) pyrene, form bulky adducts and need nucleotide excision pathways to remove the adducts. Deficiencies in cell cycle checkpoint pathways are more frequently observed in esophagus cancer than in healthy donors. Shao et al, 2006 compared the mutagen-induced damage level among individuals with different S or G2-M phase cell accumulation and observed an increase of esophageal cancer risk.

### 2.3 Oncogen p53

Oncogen p53 is a major regulator of the cell response to stress and acts as a tumor suppressor by inducing cell cycle arrest or apoptosis. Inactivation of the p53 signaling pathway has been seen in different human cancers. Previously, polymorphisms of p53 have been reported to be a possible risk factor for some types of tumors (Hrstka et al., 2009; Levine et al., 2004; Wu et al., 1998). The most common polymorphism on *p53* is at the 72<sup>nd</sup> amino acid residue with an arginine (Arg) to proline (Pro) change because of a G→C transverse. Differences in the biochemical or biological characteristics of the wild type *p53* variants have been reported. Some authors considered that the Arg72 variant can better induce apoptosis than the Pro72, indicating that the two polymorphic variants of *p53* (also so called *TP53*) are functionally distinct, which may influence cancer risk and treatment (Matlashewski et al., 1987; Thomas et al., 1999; Whibley et al., 2009). Numerous studies have reported this *p53* polymorphism in several cancers such as cervical, lung, breast, and gastric cancer (Dai et al., 2009; Dumont et al., 2003; Z. Zhang et al., 2011; Zhou et al., 2007), but its association with esophagus cancer remains elusive. Several specific molecular alterations play crucial roles in esophagus cancer, with tumor cell aneuploidy and p53 mutations being major hallmarks of both ESCC and EA (Blant et al., 2001; Fang et al., 2004; Jiang et al., 2010; Kuwano et al., 2005; Minu et al., 1994; Montesano et al., 1996; Souza, 2010; Whibley et al., 2009; Yu et al., 2007). Levine et al., 1991 considered that alteration or inactivation of p53 by mutations or interaction with oncogene products of DNA tumor viruses can lead to cancer. However, some researchers found no association between the immunomarkers p53, cyclin D1 and bcl-2 with the clinicopathological data and outcome in a selected population of esophagogastric junction adenocarcinoma patients (Lehrbach et al., 2009). The 17p is the chromosomal locus for *p53* oncogene. Studies of allelic alterations on chromosome 17p.13 and in 17p11.2-22 (microsatellite region adjacent to the *p53* locus) were performed by polymerase chain reaction (PCR) using two different primers (D17S513 and D17S514), (Table 1). An allelic alteration was observed in both tumor and non-tumor areas of esophagus cancer patients. Moreover, this dinucleotide repeat polymorphism was observed in both EA and ESCC. In addition, our studies showed statistically significant high levels of MMP-1 associated with this allelic alteration in the EA group. In the ESCC group, the allelic alteration was found associated with positive lymph nodes (Vegh et al., 2007).

Biomarker	Patients (n)	Values expressed	P	Overall survival time	References
CNR-1 <i>gene</i> (controls)	40	G/G: 60.0 % G/A: 40.0 % A/A: 0.0 %		ND	Bedoya et al. 2009a
CNR-1 <i>gene</i> ; (EC)	29	G/G: 10.8 % G/A: 61.2 % A/A: 7.9 % No a. 20.1 %		G/G: 56.3 months versus A/A: 3.5 months P=0.04	
P53 (D17S513) A/A type, EA	23	a.a.: 69.9%		ND	Vegh et al. 2007
P53 (D17S514) A/A type, EA	23	a.a.: 82.6 %		ND	
P53 (D17S513) A/A type, ESCC	14	a.a.: 50.0%		ND	Vegh et al. 2007
P53 (D17S514) A/A type, ESCC	14	a.a.: 78.6%		ND	
VEGF tumor	39	300.6±99.7pg/mg	< 0.025	P= 0.11	Bedoya et al. 2009a
VEGF no tumor	100	80.8±19.7 pg/mg			
MMP1 (EA)	23	45.6±7.6 ng/mg	< 0.05	ND	Vegh et al. 2007
TIMP1 (EA)	23	28.7±7.0 ng/mg			
MMP1 (ESCC)	14	37.0±6.9 ng/mg	= 0.44	ND	Vegh et al. 2007
TIMP1 (ESCC)	14	38.9±7.5 ng/mg			

EC: esophageal cancer; VEGF: vascular endothelial growth factor; CNR1 *gene*: cannabinoid receptor 1 gene; G/G wild type, G/A heterozygous mutation; A/A homozygous mutation; P53: oncogene p53; D17S513 and D17S514: primers used; a.a.: with allelic alterations; MMP1: Matrix metalloproteinase, TIMP: Tissue inhibitor metalloproteinase; ND: no data; No a.: with no amplification; EA: esophagus adenocarcinoma; ESCC: esophagus squamous cell carcinoma; vs.: versus; P minor than 0.05 was considered statistically significant.

Table 1. *Biomarkers in esophagus cancer*: Analysis data of different markers in tissue of esophagus cancer patients, according our some experiences.

DNA repair inhibitors are used by the cells to protect or reverse themselves against mutagens and different carcinogens. Some authors considered the small cyclin dependent kinase-inhibiting protein p21 as a critical mediator of p53 function and required for p53 - mediated growth suppression of tumor cells (Waldman T et al., 1995).

## 2.4 Cannabinoids receptors and esophagus cancer

The CB1 receptor (or CNR1) is encoded by the *CNR1* gene and located in chromosome 6q14-q15 (size 26,056 bases). CNR1 molecular function corresponds to a receptor activity and their biological processes such as signal transduction and G-protein signaling-coupled with a cyclic nucleotide second messenger (cyclic AMP). CNR1 is expressed most widely in the brain. Endocannabinoids (anandamine and 2-arachidonylglycerol) released from the neurons bind to CNR1 receptors in the pre-synaptic neurons and produce a reduction in the release of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). Cannabinoid receptors are expressed on several cell types and have functions in liver, endocrine glands, on gastrointestinal and cardiovascular activity and on pain transmission. Endocannabinoids are agonists of cannabinoid receptors and have been shown to participate in the inhibition of malignant cells, in the proliferation of cancer tissues and have been associated with different stages of the disease (Pertwee, 1997). After the receptor is engaged, multiple intracellular signal transduction pathways are activated implicating potassium ion channels, calcium channels, protein kinase A and C, Raf-1, ERK, JNK, p38, c-fos, c-jun, etc. Previously, one simple nucleotide polymorphism (SNP) was detected at nucleotide positive 1359 G→A. Due to the high polymorphism information content, this SNP is considered as a useful intragenic marker which may be related to cannabinoid system alterations. The artificial creation of an *MspI* restriction site in amplified wild type (G-allele) which is destroyed by the mutation (A-allele) has been useful to detect a silent mutation (Gadzicki et al., 1999). We have observed in *CNR1* gene 10.8 % of wild type in esophagus tissue samples of esophagus cancer patients as compared to 60.0% in *CNR1* gene in control patients (Figure 1). We

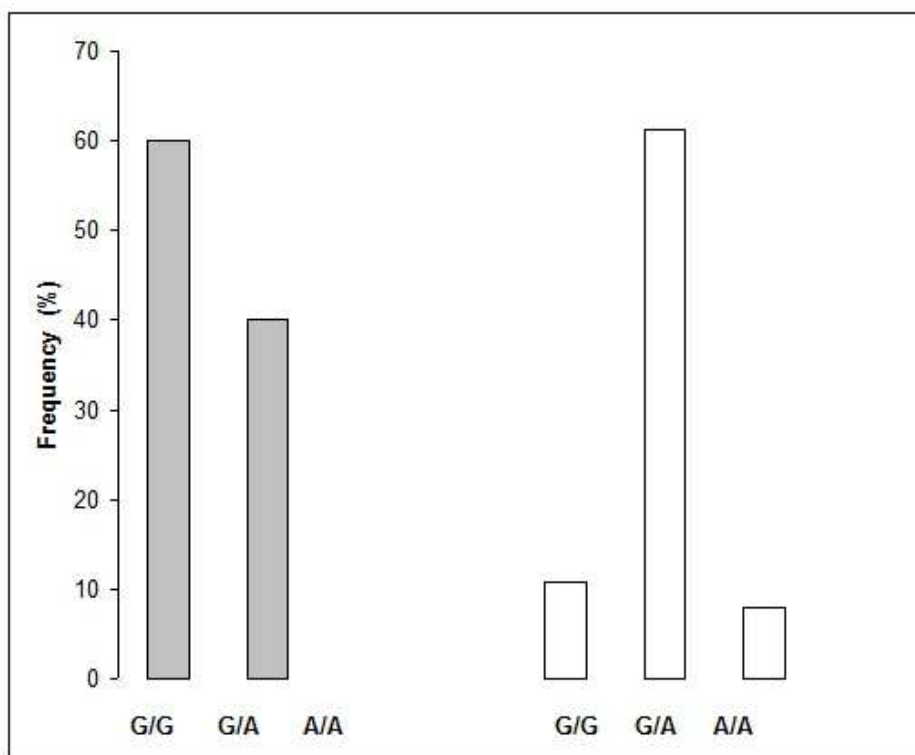


Fig. 1. Frequency of *CNR1* gene expression in esophageal tissue. Grey bars, corresponding to control healthy patients (n=40) esophagus tissue, no A/A mutation was observed. White bars, corresponding to *CNR1* gene expression in tumor of esophagus cancer patients (n=29).



concluded that this alteration may be considered as a mutation and hypothesized that this mutation is an acquired somatic mutation. Moreover, we also found that the mean survival time in wild type G/G group was longer than A/A homozygous group, ( $P=0.04$ , chi-square: 4.26) (Table 1). However, we did not find any association of *CNR-1* with the angiogenic growth factor VEGF levels. However, VEGF expression was higher in tumor than in no-tumor ( $P < 0.025$ ), but VEGF expression did not correlate with survival time. (Bedoya et al., 2009a). So, we can consider that *CNR1* gene could be considered an independent marker for survival. In addition, in colorectal cancer patients we have also found that *CNR1* gene genotype G/A plus A/A group of patients has a shorter overall survival time than G/G wild type patients (Bedoya et al., 2009b).

## 2.5 Vascular endothelial growth factor

In carcinogenesis, genetic and epigenetic changes are important for malignant transformation. The growth of solid tumors which is regulated partly by the angiogenesis process and vascular endothelial growth factor (VEGF) has been identified as the principal regulator of angiogenesis in both, physiological and pathological conditions (Ferrara, et al., 1997; Folkman, 1990). VEGF's function is to create new blood vessels during embryonic development. Binding of VEGF and other ligands to the VEGF-receptor (VEGFR) of endothelial cells activates the angiogenic pathways. VEGF is strongly expressed in many human cancers, including esophageal carcinomas (Inoue et al., 1997) and intestinal cancers (Bendardaf et al., 2008). High levels of VEGF have been associated with a poor prognosis in cancer patients. Our studies did not observe any statistically significant differences in plasma VEGF concentration in esophageal cancer patients at different clinical stages neither did in samples corresponding to different tumor and not tumor areas (Figure 2). In this study we assayed in plasma VEGF concentration of control healthy and esophagus cancer patients and the difference was not statistically significant. Analyses of VEGF expression in tumor homogenate of these patients using a cut-off level of 120 pg/mg of total protein did not appear to correlate with the overall survival time (Bedoya et al., 2009a). However, high hypoxia-inducible transcription factor-1 (HIF-1) is an important inducer of angiogenesis and VEGF expression is important as a prognostic factor and related to survival in ESCC patients (Kimura et al., 2004). Moreover, some authors considered that these factors could help to predict the response of the ESCC patients to several therapies (Shimada et al., 2002). The role of other angiogenic factors such as transforming growth factor- $\alpha$  (TGF- $\alpha$ ) and basic fibroblast growth factor (bFGF) were studied by Li et al, 2000. They suggested that TGF- $\alpha$  as well as VEGF, PD-ECGF and bFGF may be associated with angiogenesis, and progression to metastases of ESCC patients. The diagnostic of lymph node status in esophagus cancer is a very important prognostic factor. VEGF-C is a potential angiogenic factor in lymph-nodes and selectively induces vasculature in the lymphatic glands. The expression of VEGF-C has a high correlation with the lymph node metastasis in patients with stage *Tis* and *T1* of esophagus cancer patients (Tanaka et al., 2010).

## 2.6 Epidermal growth factor receptor

Epidermal growth factor (EGF) plays an important role in the cell cycle and may regulate the production of MMPs via over-expression of the epidermal growth factor receptor (EGFR). EGF protein was discovered by Stanley Cohen and Rita Levi-Montachini and both

won the Nobel Prize in 1986. EGF is a low molecular weight polypeptide of 6045-Da protein. EGF includes different biological processes such as the activation of MAPKK activity, DNA replication, chromosome organization, EGFR signaling pathway and interaction with phosphatidylinositol 3-kinase complex (PIK3R2). EGFR are on the cell surface and are activated by binding with its specific ligands (EGF, TGF $\alpha$  and others). Upon activation, EGFR undergoes a transition from an inactive to an active form. The EGFR dimerization stimulates its intrinsic intracellular protein-tyrosine kinase activity. Mutations that induce EGFR over-expression have been associated with cancer. These mutations have been the target of several treatments allowing the development of anticancer therapies such as gefitinib and erlotinib for lung cancer, cetuximab and panitumumab for colorectal cancer, as examples of a monoclonal antibody acting as inhibitors of tyrosine kinase proteins. Indeed, without kinase activity, EGFR is inactive and does not initiate the signaling cascade

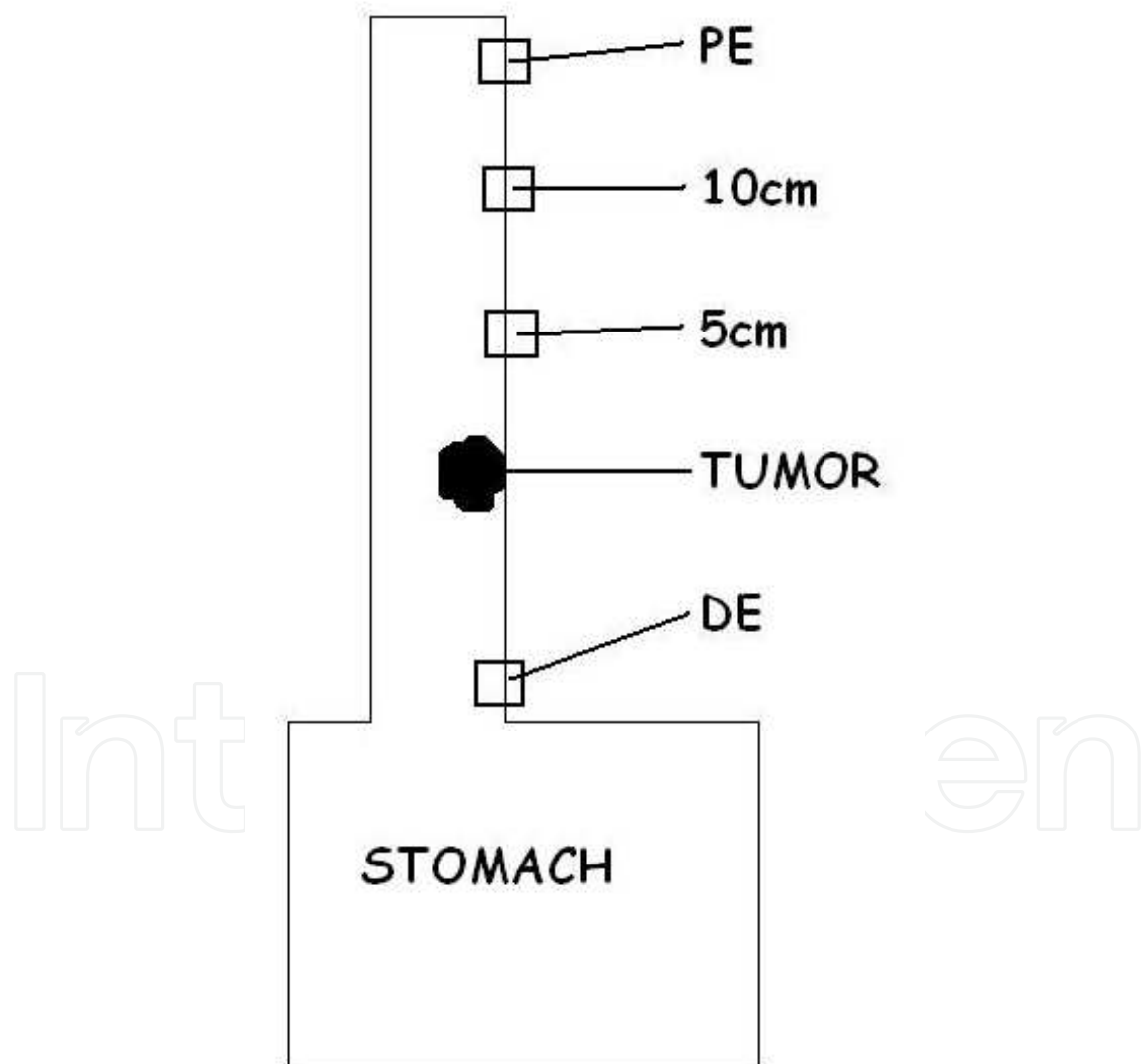


Fig. 2. Diagram of esophagus areas studied. PE: proximal edge of sample exceresis, 10 cm: sample from around tumor area; 5 com: sample around tumor area; T: tumor (EA or ESCC according to histopathologic diagnosis), DE: distal edge, sample obtained near to stomach.

pathway for growth in the cells (Lynch et al., 2004). Several studies have demonstrated that EGFR is over-expressed in tumors and ESCC cell lines. However, immunohistochemical evaluation of EGFR did not provide prognostic information for ESCC patients (Torzewski et al., 1997). The fact that EGFR correlated with age, depth of invasion, lymph node metastasis and poor prognosis was observed (Inada et al., 1999). Our results have found the over-expression of EGFR in membrane of tumor homogenate in a group of esophageal cancer patients with more than three positive lymph nodes. Nevertheless, we did not find any significant differences between mean levels of EGFR in both tumor and non-tumor areas of the esophagus (Vegh et al., 2007). EGFR over-expression and mutant *p53* tumor suppressor genes help the enrichment of a cellular subpopulation involved in epithelial to mesenchymal transition among telomerase-immortalized human esophageal epithelial cells during carcinogenesis (Ohashi et al., 2010).

### **2.7 Human chorionic gonadotropin-beta**

The human chorionic gonadotropin ( $\beta$ HCG) is a glycoprotein synthesized by normal placenta and released by the trophoblastic cells and different neoplastic cells. In esophageal tumors, by immunostaining procedures Burg-Kurland et al., 1989 observed a variation in the staining intensity of the tumor cells. Cells were weakly stained in well differentiated squamous cell carcinomas, although the poorly differentiated cells showed a more generalized pattern of staining. Moreover, these studies considered that  $\beta$ HCG is associated with ESCC as well as EA and to pre-neoplastic lesions (Burg-Kurland et al., 1989). The characteristics of this tumor marker permit the monitoring and evaluation of the treatments.

### **2.8 Carcinoembryonic antigen**

In 1965 Gold and coworkers demonstrated tumor-associated antigens in adenocarcinoma of the digestive tract in humans. The oncofetal carcinoembryonic antigen (CEA) is a glycoprotein with a molecular weight of 200,000 kDa originally isolated in colon carcinoma cells and is located on the luminal surface of the tumor cell membrane of endodermal as well as non-endodermal origin. CEA expression in serum of esophagus cancer patients is not well recognized as a biomarker. Nevertheless, correlation between CEA levels in serum and tissue was observed in patients with esophagus cancer (Sanders et al., 1994); and elevated serum CEA levels were useful for early detection of relapse in patients with EA (Kim et al., 1995). We have reported that in tissue homogenate of EA patients there were not statistically significant differences in mean levels of CEA in tumor areas when compared with non-tumor (Vegh et al., 2007). However, in ESCC tumors, CEA concentration showed statistically significant higher values in tumor samples from patients with negative lymph nodes. These results were similar to those observed in non-small-cell lung cancer patients (Vegh et al., 2002). Kosugi et al., 2004 determined the role of preoperative serum levels of CEA, CA19-9 and SCC in patients with esophagus cancer. They found that only preoperative high levels of serum SCC antigen indicate an adverse outcome after esophagectomy and the appearance of distant metastases (Kijima et al., 2000; Kosugi et al., 2004). In summary, the CEA marker is very useful for monitoring previously diagnosed cancer.

## 2.9 Interleukins

Interleukins (IL-1 through IL-17) are a group of cytokines that participate in stimulating the immune response in inflammation and in hematopoiesis. Interleukins are a group of cellular messenger molecules, so called cytokines, which act as modulators of cellular behavior and are secreted rapidly by cells in response to several stimuli such as an infectious agent. The first interleukin was identified in the 1970s (Gillis et al., 1978). Different types of interleukins have become known since then and are designated numerically. IL1 and IL2 are responsible for activating T and B lymphocytes. IL-1, along with IL-6, is also a mediator of inflammation. IL-6 expression at local tumor sites or in systemic circulation has been associated with disease progression and poor prognosis of esophageal cancer and may act as a resistance factor against cisplatin-based treatments (Suchi et al., 2011). The clinicopathological significance of IL-6 and other cytokine levels in esophageal cancer was associated with a poor outcome (Motoyama et al., 2011; Xin et al., 2010; H.Y. Zhang et al., 2011).

## 2.10 microRNAs

The expression of the miR-17-92 cluster was first shown in ESCC and is over-expressed in 75% of esophageal cancer patients (Liu et al., 2011). In addition, its over-expression could promote cellular growth in vivo and in vitro. Furthermore, antisense oligonucleotides (ONs) inhibited miR-19a and induced apoptosis while miR-17-5p, miR-18a, miR-20a and miR-92-1 were not affected. It was found that antagomir-19a treatment could impair tumor growth in vivo. In fact, using Human Apoptosis RT2 Profiler PCR Array 384HT was observed that tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) was 12-fold up-regulated in cells transfected with miR-19a antisense ONs compared to the cells treated with the control scramble ONs. miR-19a was predicted to target the 3' untranslated region of TNF- $\alpha$  mRNA and this was confirmed by luciferase reporter assay. Taken together, they conclude that the miR-17-92 cluster is over-expressed in ESCC and that TNF- $\alpha$  could be a novel target of miR-19a (Liu et al., 2011).

## 2.11 c-erbB-2 or HER2 gene

HER-2/neu (c-erbB-2, HER2) gene amplification and protein over-expression have been associated with poor prognosis in several solid tumors, including breast and gastric cancer. However, its incidence and significance in EA is unknown (Thompson et al., 2011). Expression of erb-B2 in esophageal cancer patients was associated with longer survival and may be a good marker to monitoring the treatment sensitivity (D'Amico and Harpole, 2000).

## 2.12 TGF-alpha

Transforming growth factor-alpha (TGF- $\alpha$ ) is produced by several human carcinomas. TGF- $\alpha$  maps to human chromosome 2p11-2p13. TGF- $\alpha$  is a small protein of 50 amino acids. This growth factor is found in plasma and urine and is produced by some non-transformed cells during the development such as, keratocytes, macrophages, platelets and hepatocytes. Their synthesis is induced by estrogens and is related to EGF. The biological activities of both growth factors are very similar and both bind to the same membrane receptor encoded by the cellular *erb* oncogene. Experimental studies in Wistar rats observed that TGF- $\alpha$  and EGFR play crucial roles in chronic reflux esophagitis (Fujiwara et al., 2004). The integrity of

esophageal mucosa, acts upon the equilibrium between cellular protective mechanisms and different aggressive factors. It has been found that human esophageal submucosal glands elaborate protective biomarkers like TGF- $\alpha$ , EGF, prostaglandin E(2), bicarbonate and no-bicarbonate buffers (Sarosiek and McCallium, 2000). Nevertheless, an increased production of TGF- $\alpha$  is associated with malignant transformation in different cell types (Li et al., 2000). TGF- $\alpha$  can be assayed in plasma by a specific radioligand assay or the ELISA method and by colony formation assay. Aloia et al., 2001, analyzed the expression of the tumor markers P-gp, p53, and TGF- $\alpha$  in node-negative esophagus cancer patients. Their results showed that this type of analysis sustains the immunohistochemical prognostic value.

### 2.13 TGF-beta

Transforming growth factor beta (TGF- $\beta$ ) and Notch signaling pathways play important roles in regulating self-renewal of stem cells and cell-fate determination. Both pathways are frequently implicated in gastrointestinal carcinogenesis. TGF- $\beta$ 1 mediated the mesenchymal-epithelial transition and may be relevant in esophageal carcinogenesis (Rees et al., 2006; Thiery, 2002). However, others showed that the contribution of TGF-beta to esophageal adenocarcinoma remains associated with EGFR and p53 (Ohashi et al, 2010). It is well known that the stromal compartment plays an important role in carcinogenesis. Genetic analysis showed a strong contribution of an inflammatory component and the key pathways included cytokine-cytokine receptor interactions and TGF- $\beta$  in BE disease progression and how these can affect the outcome or progression (Saadi et al. 2010).

### 2.14 Alpha fetoprotein

Alpha fetoprotein (AFP) is a glycoprotein of 591 aminoacids and a carbohydrate moiety. AFP is highly expressed in human fetus but in adults, AFP levels are low with unknown function, although it can be used as a biomarker to detect tumors. It is indicative of germ-cell tumors, hepatocellular carcinoma and ectopic production of AFP has also been found in different tumors. In some tumors, the decrease of AFP levels indicates a good prognostic value. AFP expression is elevated in gastrointestinal malignancies and its expression is related to metastasis (Liu et al., 2010; Mizejewski, 2002). In summary, this tumor marker is very useful for monitoring previously diagnosed cancer.

### 2.15 CA 19-9

The carbohydrate antigen 19-9 (CA 19-9) tumor marker can be detected in blood serum and in the tumor homogenate of different cancer patients. Levels are often elevated in some gastrointestinal cancers, such as colorectal, pancreatic and esophagus cancer. As previously reported by our group, the level CA 19-9 was detected by ELISA in colorectal cancer patients and was considered as an independent prognostic factor for the relapse (Morales-Gutierrez et al, 1999). Studies performed in serum of human ESCC patients showed that CA19-9 is a link for E-selectin and this association may play an important role in tumor metastasis. Serum CA19-9 may be useful in the follow-up of recurrence and response to treatment (Mcknight et al, 1989; Oshiba et al, 2000). In EA patients, we observed a higher concentration of CA 19-9 in tumor areas than in non-tumor areas from the same patient, but these results did not correlate with their clinical characteristics (Vegh et al, 2007).



Nevertheless, CA 19-9 concentration was higher in patients with more than three positive lymph nodes than in patients with negative nodes. In ESCC patients, CA 19-9 concentration did not show any differences between tumor and non-tumor areas. In conclusion, patients who had advanced or metastatic cancer can be monitored by their CA 19-9 levels throughout the treatment.

### **2.16 Tumor Necrosis Factor $\alpha$**

Tumor necrosis factor alpha (TNF- $\alpha$ ) is a pro-inflammatory cytokine with conflicting effects in both, tumor growth and tumor regression. These paradoxical results seem to be related to differences in this cytokine concentration, as high therapeutic doses induced tumor regression while physiological levels of endogenous TNF- $\alpha$  promote tumor growth (Anderson et al., 2004). Clinical data related to TNF- $\alpha$  expression by esophageal cells are limited. Kilic et al. 2009, studied TNF- $\alpha$  and IL-2 expression in the distal esophageal muscle in patients with achalasia of the esophagus and observed that the proportion of inflammatory cells expressing TNF- $\alpha$  is inversely correlated with the duration of the clinical symptoms. Other studies have shown that TNF- $\alpha$  is up-regulated in the progression to Barrett's metaplasia suggesting a role of TNF- $\alpha$  in the transcription of gastrointestinal oncogenes (Tselepis et al., 2002). In ESCC where the miR-17-92 cluster is over-expressed, TNF- $\alpha$  seems to be a novel target of miR-19a (Liu et al., 2011).

## **3. Esophageal cancer and stem cells**

Despite the fact the incidence of EA has increased over the last 40 years, the biology of the normal esophageal epithelium and the pathogenesis of esophageal cancer is not well understood (Nguyen et al., 2011). Currently, it is still unknown if esophageal cancer initiation, growth and maintenance is caused: i) by the "clonal selection theory", i.e., through the accumulation of genetic alterations in some cells that acquire growth advantage over normal cells and leads to the selection of these clones; ii) by the "cancer stem cell (CSC) theory" based in the suggestion that only a small number of stem cells accumulate the genetic alterations and contribute to the esophageal tumor growth and maintenance; or iii) by a mixture of both models (Adams and Strasser, 2008; Hormi-Carver and Souza, 2009).

### **3.1 Cancer Stem Cell (CSC) theory and esophageal cancer**

CSC theory is based on the idea that most cancers are initiated for stem cells with genetic alterations that are unable to undergo terminal differentiation, i.e., the proliferation capacity of stem cells can be difficult to control under certain circumstances and contribute to the tumor formation (Nguyen et al., 2011; Quante and Wang, 2009). In solid tumors including esophageal cancer, the CSCs have been correlated with resistance to chemotherapy and radiation, recurrence and metastasis (Zhang et al., 2005). It is interesting to highlight the lack of agreement on the best markers for CSCs in digestive tumors and doubts about the real phenotype and also the existence of the CSCs (Quante and Wang, 2009). There is little evidence for the existence of CSCs in esophageal cancer. Stimulation of esophageal stem cells of the epithelium contributes to both, esophageal epithelial regeneration and cancer. Changes in the activity of the esophagus stem cells and the up- or down-regulation of stem cell markers appear to be related to esophageal cancer development, tumor progression and

final clinical outcome. Further understanding and characterization of adult esophageal stem cells and the factors that contribute to the development of dysplasia and malignancy it is a matter of critical importance (Croagh et al., 2008).

### 3.2 Stem cells in the esophagus

Stem cells are classified in two general groups as embryonic and adult stem cells. They have the ability to regenerate the tissue where they reside because of their characteristics of self-renewal and multipotency. Adult stem cells within the gastrointestinal tissue are classified as esophageal, gastric, intestinal, colonic, hepatic and pancreatic (Quante and Wang, 2009).

Stem cells in the human esophagus are present in the basal layer of the stratified squamous epithelium (Kalabis et al., 2008; Seery and Watt, 2000). Human esophagus is a complex tissue with a slow cell turnover (Croagh et al., 2008). A population of stem cells known as Side Population cells (SP cells) were isolated from mouse esophagus (Epperly et al., 2004; Kalabis et al., 2008). Esophageal SP cells have the ability to home in on and differentiate to esophagus cells as shown by *in vitro* and *in vivo* esophageal injury models. A rare stem cell population expressing high levels of  $\alpha_6$ -integrin and low levels of CD71 was characterized in the basal layer of the mouse esophagus and whose final function is to form and/or regenerate the suprabasal layers (Croagh et al., 2007). A population of stem cells characterized by low expression of  $\beta 1$ -integrin and high expression of  $\beta 2$ -laminin chain was isolated from the human esophagus with the ability to reconstitute the esophageal epithelium *in vitro* (Seery and Watt, 2000). It has also shown that bone marrow stem cells may contribute to cell regeneration of normal and injured rat esophagus (Sarosi et al., 2008).

### 3.3 Stem cell markers involved in cancer development and evolution

It is a matter of crucial importance to know the markers characteristics of stem cells whose expression is significantly increased in the esophageal cancer cells and that would be involved in cancer development and associated with a poorer clinical outcome. However, there is little information about the phenotype and the biology of the stem cells and the cancer stem cells responsible of the low five-year survival rate in esophageal cancer (Kalabis et al., 2008; Nguyen et al., 2011).

The CD44, a glycoprotein involved in cell motility and migration, is one of the most used markers for the identification of CSCs in multiple tissues (Nguyen et al., 2011; Quante and Wang, 2009). CD44 is also a marker of esophageal CSCs and its expression is associated with metastasis and a poor prognosis (Takayama et al., 2003). However, CD133, another common CSC marker was not expressed in EA stem cells (Grotenhuis et al., 2010).

SP cells in the esophagus presented CSCs characteristics indicated by higher clone formation efficiency, up-regulation of stem-cell related genes such as Oct-4 and Sox-2, up-regulation of the ABC transporter genes, increased expression of the Notch and Wnt-related genes and a higher expression of beta-catenin protein (Epperly et al., 2004; Huang et al., 2009).

Analysis of tumors obtained from ESCC patients demonstrated a high expression of Oct-4 and Sox-2 genes and this expression was significantly associated with a higher histological grade and poorer clinical outcome (Bass et al., 2009; Wang et al., 2009; X. Zhou et al., 2011). The HIWI gene was identified in hematopoietic stem cells and germ cells and plays a role in

stem cell pluripotency, self-renewal and differentiation. HIWI was also detected in human ESCC and its over-expression was associated with higher histological grade and poorer overall survival (He et al., 2009).

Musashi-1 is a RNA-binding protein identified as a marker of the intestinal stem cells and found in BE and significantly increased in EA, whereas it is absent in normal squamous epithelium indicating an important role in the development and maintenance of the esophagus diseases or even the cell of origin for esophagus cancer (Bobryshev et al., 2010).

Leucine-rich-repeat-containing G-protein-coupled receptor (LgR5) was first proposed as an intestinal stem cell marker and recently identified in EA but not in ESCC patients. LgR5 expression is related with the low survival rate in these patients (von Rahden et al., 2011). The neural stem cell marker low-affinity neurotrophin receptor p75NTR is expressed in esophageal keratinocyte stem cells with high proliferation properties (Okumura et al., 2003). This marker was present in an elevated number of ESCC and EA patients (Okumura et al., 2006; Sun et al., 2009). p75NTR could be a potential target for future specific esophageal therapies.

### **3.4 Adult stem cells as an approach for the treatment of gastrointestinal diseases**

In recent years, the progress in stem cells identification and characterization indicate the potential therapeutic applications of stem cells in regenerative medicine for the treatment of several pathologies. The different types of stem cells, embryonic, induced pluripotent and adult stem cells are emerging as a potential approach to treat gastrointestinal disorders. Stem cells could be classified in two main groups, i.e., embryonic and adult stem cells. There is an increasing interest in the potential use of stem cells in regenerative medicine.

#### **3.4.1 Embryonic stem cells**

Embryonic stem cells (ESCs) have a high proliferation and differentiation capacity (pluripotency). However, there are several limitations to their use for therapeutic purposes including the ethical considerations, the elevated self-renewal properties that will induce tumors and the immune rejection as they are not patient-derived (Ao et al., 2011).

The induced pluripotent stem cells (iPSCs) are stem cells obtained from somatic stem cells by transfer of exogenous genes involved in the maintenance of ESCs. The iPSCs can be generated from the patients' somatic cells preventing the immune rejection. However, like ESCs the risk of teratoma formation is an important problem to be overcome for future clinical application (Kooreman and Wu, 2010).

#### **3.4.2 Adult stem cells**

Adult stem cells are undifferentiated cells present a tissue or organ in very small amounts that can renew by themselves and differentiate into all of the specialized cell types of the tissue or organ. The principal role of adult stem cells is to maintain and repair the tissue in which they are found in case of any disease or injury. Adult stem cells have been found in almost all adult tissues, even in more tissues than was thought possible. Several adult stem cells such as adult hematopoietic stem cells from bone marrow or from umbilical cord blood have been used in transplants for 40 or 20 years, respectively.

Mesenchymal stem cells (MSCs) are adult stem cells also present in bone marrow. These non-hematopoietic stem cells are isolated from bone marrow by their adherence to the plastic plates after culture and characterized by the expression of a set of markers (CD105, CD73 and CD90) and the lack of expression of hematopoietic markers (CD45, CD34, CD14 or CD11b, CD79a or CD19) and the HLA class II surface molecules (Dominici et al., 2006). MSC are multipotent cells with the capacity of differentiation into bone, fat and cartilage (Horwitz et al., 2005). In addition to the mesodermal differentiation, MSC have been differentiated to cells of the endodermal and ectodermal embryonic layers. This differentiation capacity as well as their immunosuppressive and immunomodulatory properties makes MSCs a very attractive resource for tissue regeneration (Liu et al., 2009). Bone marrow MSC are the most used cells in both experimental and clinical settings, although MSCs have been isolated from numerous sources such as adipose tissue, umbilical cord blood, umbilical cord tissue, amniotic fluid and placenta (Broxmeyer et al., 2006; De Coppi et al., 2007; Igura et al., 2004; Macias et al., 2010; Miki et al., 2005; Sarugaser et al., 2005; Soncini et al., 2007; Tallone et al., 2011).

Human placenta is an especially complex organ composed of both fetal and maternal tissues. At the time of birth, placenta loses its function and is normally discarded. MSC obtained from human placenta are stem cells without ethical concerns, isolated without invasive procedures and present low risk of viral infection (Hemberger et al., 2008; Pappa and Anagnou, 2009; Parolini et al., 2008). Recently, we have described the isolation and characterization of a population of MSCs from the maternal part of human placenta, i.e. decidua parietalis (Macias et al., 2010). The cells named Decidua-derived Mesenchymal Stem Cells (DMSC) is a homogeneous population of MSCs that showed high proliferation and differentiation capacity into cell types from the three embryonic layers, genomic stability and until senescence and a decrease in telomerase activity indicating that DMSCs could be safely used in regenerative medicine. In addition, DMSCs are hypo-immunogenic cells suggesting that they could be used in both, autologous and allogenic transplantation for future clinical trials.

### **3.4.3 Mesenchymal stem cells for the treatment of gastrointestinal diseases**

Recent studies have revealed that MSCs selectively migrate and home in on to damaged tissues and organs after systemic or local application (Kidd et al., 2009). This tropism for sites of injury, irrespective of the tissue or organ, indicates that MSCs can be useful as cellular vehicles as tumors are considered as “wounds that never heal” (Dvorak, 1986). Indeed, bone marrow stem cells migrate to esophageal epithelium and contribute to tissue regeneration under normal and/or pathological conditions (Sarosi et al., 2008). These migratory properties make MSCs a useful and efficient tool for the delivery of therapeutic anti-tumor genes to the tumor area (Hall et al., 2007). MSCs will later produce and release the anticancer agents in situ which would significantly increase the efficacy and decrease the side effects of these therapeutic agents (Nakamizo et al., 2005; Studeny et al., 2002; Studeny et al., 2004). Besides, these authors showed also evidences that MSCs can also be used as therapeutic agents themselves. The use of MSCs as cellular delivery vehicles offer several advantages such as MSCs from several sources are easy to isolate and culture; can be expanded in culture without losing their characteristics; and are hypoimmunogenic and



show immunomodulatory properties to be well tolerated in allogeneic transplantation (Horwitz et al., 2005; Macias et al., 2010).

#### 4. Conclusion

In EA and ESCC patients, standard treatments are similar although it is necessary to develop earlier diagnosis because of the poor prognosis of esophageal cancer compared to other digestive cancers. It is necessary to select the most appropriate predictive biomarkers – especially, those assayed in esophageal tissue- and determined in with the aim of designing specific treatments for each type of esophagus cancer patients and obtain a clear clinical benefit. The overall expression of a set of single markers together with the clinical data would be useful to predict the development and evolution of this type of tumors.

In the near future, integrated approaches to biomarkers discovery and development, analyses and simulations to predict and identify the most specific biomarkers in esophagus cancer, are necessary. In addition, will be important bioinformatics analyses and tissue array studies (genomic, proteomic and transcriptomic-based biomarkers) with high quality clinical samples.

The molecular and cellular events responsible for regulating both, the replacement of the normal esophageal epithelium and the development and maintenance of cancer are not well understood. It is important to understand how the stem cells fate is regulated and the factors that play a role in its de-regulation and will contribute to the formation of a tumor. MSCs contribute to the regeneration of several tissues and could be used as cellular vehicles of anti-cancer drugs increasing their efficacy and decreasing the side effects which would greatly improve the quality of life of esophagus cancer patients. In summary, understanding the biology of normal esophageal epithelium and the role of the biomarkers of tumor, non-tumor and esophageal stem cells it is crucial for designing more specific therapies in order to increase the reduced current clinical outcomes of esophagus cancer patients.

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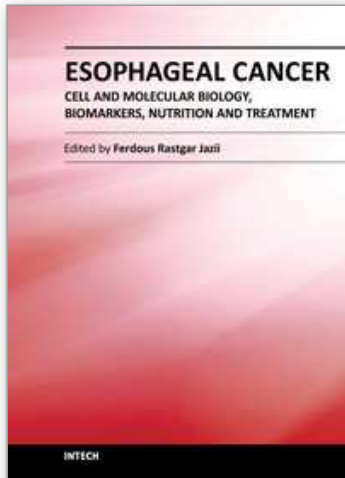
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**Esophageal Cancer - Cell and Molecular Biology, Biomarkers, Nutrition and Treatment**

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

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**How to reference**

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

Irene Vegh and Ana I. Flores (2012). Biomarkers, Stem Cells and 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/biomarkers-stem-cells-and-esophageal-cancer>

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