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The Role of Tumor Microenvironment in Oral Cancer

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1. Introduction

Human oral squamous cell carcinoma (HOSCC) is the most common malignant neoplasm arising in the mucosa of the upper aerodigestive tract. It is an aggressive tumor that is difficult to treat with conventional therapies, including chemotherapy, radiation, and surgery. Because surgical treatment often affects profoundly the quality of life and activities of daily living of the affected patients with HOSCC, and thus new therapeutic strategies are necessary along with the other conventional therapy.

In recent years considerable progress has been made in understanding the genetic basis of the development of HOSCC. It is well established that an accumulation of genetic alterations is the basis for the progression from a normal cell to a cancer cell, referred to as multi-step carcinogenesis (Califano et al., 1996). Progression is enabled by the increasingly more aberrant function of genes that positively or negatively regulate aspects of proliferation, apoptosis, genome stability, angiogenesis, invasion and metastasis (Hanahan et al., 2000). Gene function can be altered in different ways: tumor suppressor genes may be inactivated by mutation, deletion or methylation and oncogenes can be activated by mutation or amplification. A description of these alterations and how these are detected has previously been described (van Houten et al., 2000, Reid et al., 1997, Braakhuis et al., 2002). Oral cancers are characterized by a multitude of these genetic alterations and ongoing research is focusing on identifying the critical genetic events and the order in which they occur during carcinogenesis. Frequently occurring genomic alterations are supposed to contain the genes that are the most important for the development of a certain type of cancer (Albertson et al., 2003). Common alterations for oral cancer are inactivation of TP53 (located at 17p13), gain of chromosomal material at 3q26 and 11q13, and losses at 3p21, 13q21 and 14q32 (Gollin, 2001, Forastiere et al., 2001). For most of these regions the putative tumor suppressor genes or oncogenes still need to be identified. In general, loss of chromosomal material (allelic losses) at 3p, 9q and 17p was observed in a relatively high proportion of dysplastic lesions and therefore these alterations were interpreted to be early markers of carcinogenesis. Several studies suggest, however, that early genetic changes do not necessarily correlate with altered morphology.

Although recent improvements in the diagnosis and treatment of malignant tumors have extended the average length of patients' lives, the incidence of multiple primary malignant tumors is increasing (Licciardello et al., 1989). In particular, it has been reported that patients with head and neck cancer often develop multiple primary neoplasms (Sakashita et al., 1996). This phenomenon has been attributed to 'field cancerization', a concept based in the hypothesis that prolonged exposure to certain risk factors, such as tobacco products, leads to the independent transformation of multiple epithelial cells at several distinct anatomic sites (Slaughter et al., 1953). In addition, it is now becoming clear that the tumor microenvironment, which is largely orchestrated by inflammatory cells, is an indispensable participant in the neoplastic process, fostering proliferation, survival and migration. Recent data have expanded the concept that tumor microenvironments including hypoxia, and inflammation that are the critical components of tumor progression. Many cancers arise from sites of infection, chronic irritation and inflammation. Many tumors also contain hypoxic microenvironments, a condition that is associated with poor prognosis and resistance to treatment (Helmlinger et al., 1997).

On the other hand, as is obvious, host has defense mechanisms against various carcinogenesis events like above. Host professional antigen-presenting cells (APCs) appear to play an important role in the presentation of tumor antigens and the induction of specific immune responses to tumors, a role that was initially attributed entirely to the tumor cells themselves (Huang 1994, Rock et al., 1993). However, despite their expression of these distinct APCs, attempts by the immune system to eliminate a tumor are often ineffective. It has recently been reported that in cancer patients the tumor cells themselves may also evade immune attack by expressing immunosuppressive cytokines.

Thus, oral carcinogenesis is a highly complex multifactorial process that takes place when epithelial cells are affected by several genetic alterations. The use of molecular biology techniques to diagnose oral cancerous lesion might be markedly improved the detection of alterations that are invisible under the microscope.

This chapter presents up-to-date evidence on molecular markers into the tumor microenvironment that have involved in the proliferation and progression mechanisms of the oral cancer.

2. Role of myelomonocytic cells in tumor microenvironment

Myeloid cells including monocytes and macrophages are key elements which regulate tissue homeostasis and local inflammation/immunity, differentiating into various cell types in response to provocative stimuli (Zeh et al., 2005, Demaria et al., 2010).

Monocytes exist as the second recruited effectors of the acute inflammatory response after neutrophils and also migrate to the site of tumor microenvironment, guided by chemotactic factors. It is known that monocytes, in the presence of granulocyte–macrophage colony stimulating factor (GM-CSF) and interleukin (IL)-4, differentiate into immature dendritic cells (DCs) (Talmor et al., 1998). DCs migrate into inflamed peripheral tissue where they capture antigens and, after maturation, migrate to lymph nodes to stimulate T-lymphocyte activation. Soluble factors such as IL-6 and M-CSF, derived from neoplastic cells, push myeloid precursors towards a macrophage-like phenotype (Allavena et al., 2000).

DCs are the most effective APCs in the induction of primary immune responses (Steinman 1991, Knight et al., 1993) and are considered to be the best vehicle for the delivery of tumor-

specific antigens in cancer immunotherapy (Austin 1993, Zitvogel et al., 1996, Mayordomo et al., 1995, Hsu et al., 1996). The existence of DCs in cancer-bearing hosts has attracted a great deal of interest because of their potential significance for tumor immunity. However, despite their expression of these distinct APCs, attempts by the immune system to eliminate a tumor are often ineffective. It has recently been reported that in cancer patients the tumor cells themselves may also evade immune attack by expressing immunosuppressive cytokines such as interleukin IL-10, transforming growth factor (TGF)-β1, receptor-binding cancer antigen expressed on SiSo cells (RCAS1), IL-23, and vascular endothelial growth factor (VEGF), which induce defective immune cell function and a defective host immune response (Gabrilovich et al., 1996, Gabrilovich et al., 1998, Buelens et al., 1995, Mitra et al., 1995, Brooks et al., 1998). Several studies have also described the defective function of APCs, including macrophages, DCs, and B cells, in tumor-bearing hosts (Tan et al., 1994, Watson et al., 1995, Alcalay et al., 1991, Erroi et al., 1989). A proposed mechanism for the inhibition of the activation of high-potency DCs ex vivo is represented in **Fig. 1**.

Monocytes, which also differentiate into macrophages in tissues, are next to migrate to the site of tissue injury, guided by chemotactic factors. Once activated, macrophages are the main source of growth factors and cytokines, which profoundly affect endothelial, epithelial and mesenchymal cells in the local microenvironment.
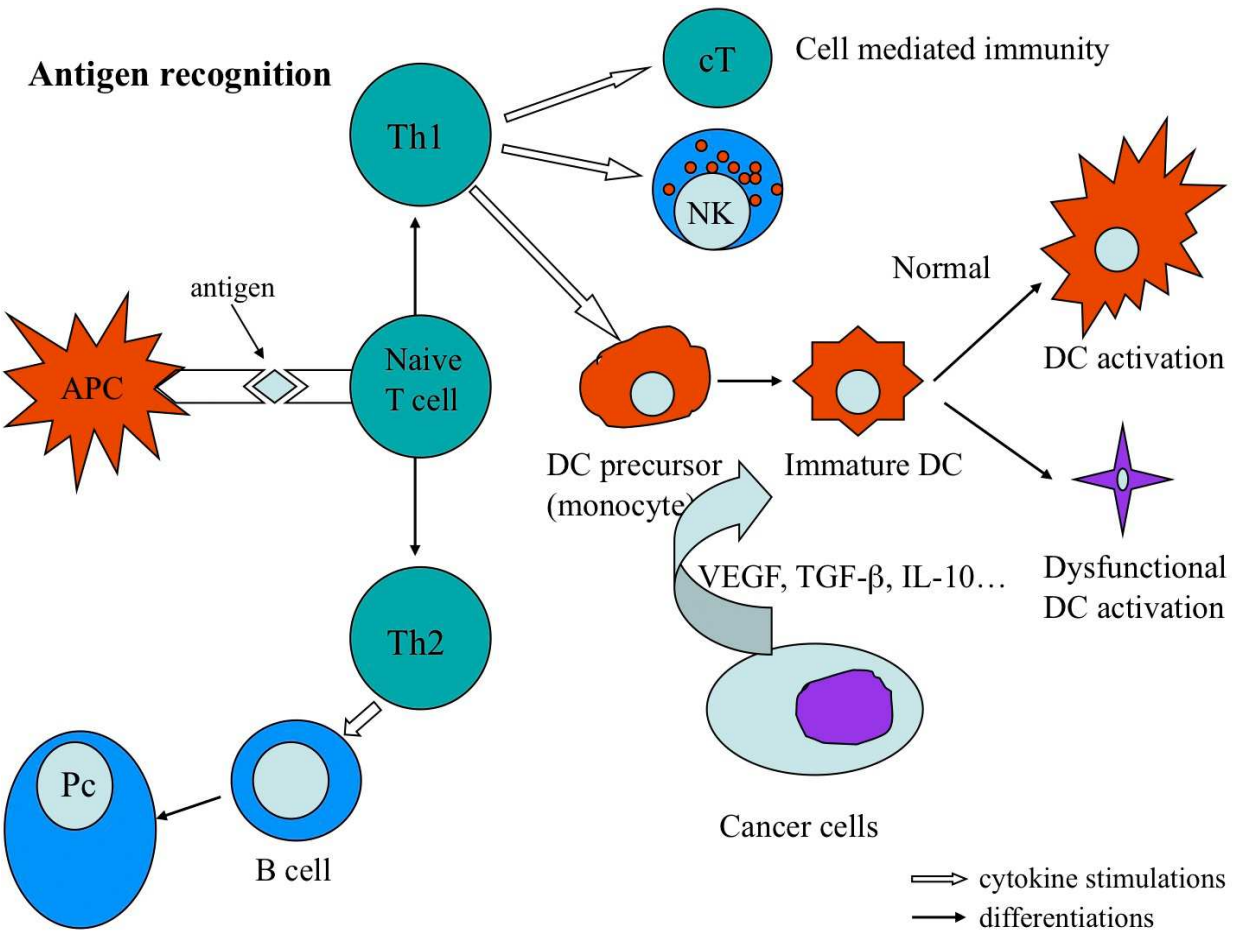

Fig. 1. A proposed mechanism for the DC activation and dysfunctional DC activation during the ex vivo. APC: antigen presenting cells, Th: helper T cell, cT: cytotoxic T cell, NK: Natural killer cell, DC: dendritic cell, Pc: plasma cell.

3. Role of cytokines in tumor microenvironment

The reciprocal interactions between tumor cells and their microenvironment — extracellular matrix (ECM), growth factors, fibroblasts, immune and endothelial cells — play an essential role in the earliest stages of transformation to malignant progression and metastasis (Nyberg et al., 2008). Particularly, fibroblasts have many prominent roles in the cancer progression. In fact, in many carcinomas, the majority of the stromal cells are fibroblasts that possess myofibroblastic characteristics and are called cancer-associated fibroblasts. They produce ECM molecules, proteases, growth factors, and chemokines that crucially affect the carcinoma cell behavior (Kalluri et al., 2006, Orimo et al., 2006). Furthermore, the causal relationship between chronic inflammation, innate immunity and cancer is now widely accepted, and the similarities in the regulatory mechanisms have been suggested for more than a century. Many cancers arise at the site of chronic inflammation and inflammatory mediators are often produced in tumors. The frequent use of anti-inflammatory drugs reduces the incidence of a variety of human tumors. Although blockading some of these mediators has been shown to be efficacious in experimental settings, it is still unclear whether the inflammatory reaction at the tumor site promotes tumor growth or simply implies the failed attempt of the immune system to eliminate the rising malignancy.

Neutrophils (and sometimes eosinophils) are the first recruited effectors of the acute inflammatory response. Monocytes, which differentiate into macrophages in tissues, are next to migrate to the site of tissue injury, guided by chemotactic factors. Once activated, macrophages are the main source of growth factors and cytokines, which profoundly affect endothelial, epithelial and mesenchymal cells in the local microenvironment. Mast cells are also important in acute inflammation owing to their release of stored and newly synthesized inflammatory mediators, such as histamine, cytokines and proteases complexed to highly sulphated proteoglycans, as well as lipid mediators. Thus, we have considered that various cytokines play the very important role by forming the cytokine cascades in the tumor microenvironment of the oral cancer.

3.1 Receptor-binding Cancer Antigen expressed on SiSo cells (RCAS1)

RCAS1 is a type II membrane protein isolated as a human tumor-associated antigen by a mouse monoclonal antibody (22-1-1 antibody) against a human uterine adenocarcinoma cell line, SiSo (Sonoda et al., 1995). RCAS1 acts as a ligand for a putative receptor present on immune cells such as T, B and NK cells and inhibits the growth of receptor-expressing cells, further induces apoptotic cell death (Nakashima et al., 1999). These observations suggest a role of RCAS1 in the immune escape of tumor cells. A variety of cancer tissues have been screened (Sonoda et al., 1996, Sonoda et al., 1998, Iwasaki et al., 2000, Izumi et al., 2001, Kubokawa et al., 2001, Noguchi et al., 2001, Takahashi et al., 2001, Hiraoka et al., 2002, Nakakubo et al., 2002, Fukuda et al., 2004) and were found to be positive for RCAS1 expression, including human uterine, ovarian, esophageal SCCs, pancreatic adenocarcinomas, hepatocarcinomas, skin SCCs, gastric adenocarcinomas, lung cancer cells and HOSCCs, but not in normal tissues.

We investigated whether tumor cells which are expressing RCAS1, induce apoptosis in its receptor-positive cells, PBLs. The apoptotic index (AI) of TILs was also examined in HOSCC

tissues. The correlations between RCAS1 expressions and clinicopathological variables in HOSCC and adenoid cystic carcinoma (ACC) tissues were examined, respectively. As the results, it was demonstrated that RCAS1 was frequently expressed both in HOSCC and ACC, *in vitro and vivo,* and its function on KB cells clearly led apoptosis to PBLs *in vitro* (Fukuda et al., 2004). Our results indicated that RCAS1 expression plays a key role in the immune escape mechanism of oral cancer, thus that RCAS1 expression could be used as a predictor of poor prognosis in patients with oral cancer. Further investigation of the role of RCAS1 will be required to clarify RCAS1-mediated tumor survival and to establish a strategy of RCAS1-based oral cancer therapy.

3.2 Interleukin (IL)-12 & IL-23

The causal relationship between chronic inflammation, innate immunity and cancer is now widely accepted, and the similarities in the regulatory mechanisms have been suggested for more than a century (Balkwill et al., 2001, Coussens et al., 2002). Many cancers arise at the site of chronic inflammation and inflammatory mediators are often produced in tumors (Coussens et al., 2002, Balkwill et al., 2005). The frequent use of anti-inflammatory drugs reduces the incidence of a variety of human tumors (Zha et al., 2004). Although blockading some of these mediators has been shown to be efficacious in experimental settings, it is still unclear whether the inflammatory reaction at the tumor site promotes tumor growth or simply implies the failed attempt of the immune system to eliminate the rising malignancy.

IL-23, a heterodimeric cytokine with many similarities to IL-12, has recently been identified as a factor linking tumor-associated inflammation and a lack of tumor immune surveillance (Langowski et al., 2006). IL-23 comprises a p19 subunit that associates with the IL-12p40 subunit (Oppmann et al., 2000), whereas IL-12 is a combination of IL-12p35 and the same IL-12p40 subunit (Sospedra et al., 2005). Although p19 is expressed in various tissues and cell types, it lacks biological activity and only becomes biologically active when complexed with p40, which is normally secreted by activated macrophages and DCs (Oppmann et al., 2000). IL-23 uses many of the same signal-transduction components as IL-12, including the IL-12 receptor (R) β1 subunit (IL-12Rβ1), Janus kinase (Jak)2, Tyk2, signal transducer and activator of transcription (Stat)1, Stat3, Stat4, and Stat5 (Oppmann et al., 2000, Parham et al., 2002). IL-23R, composed of the IL-12Rβ1 and the IL-23R subunit, is also expressed in DCs, macrophages, and T cells (Parham et al., 2002). Consistent with the structural and biological similarities of IL-12 and IL-23, the IL-23R complex shares a subunit with that of IL-12 (IL-12Rβ1), however, it does not use or detectably bind to IL-12Rβ2 (Oppmann et al., 2000). The ability of cells to respond to either IL-12 or IL-23 is determined by expression of IL-12Rβ2 or IL-23R, respectively (Parham et al., 2002). Upon engaging IL-23, IL-12Rβ1 and IL-23R associate, marking the beginning of the IL-23 signal-transduction cascade, many of whose components are now known (**Fig. 2**).

Additionally, both cytokines promote the T helper cell type 1 (Th1) costimulatory function of antigen-presenting cells (Lankford et al., 2003) (**Fig. 3**).

However, IL-23 does differ from IL-12 in the T cell subsets that it targets. IL-12 acts on naive CD4+ T cells, whereas IL-23 preferentially acts on memory CD4+ T cells (Lankford et al., 2003). It has been reported that IL-12 has potent antitumor activity in a variety of murine
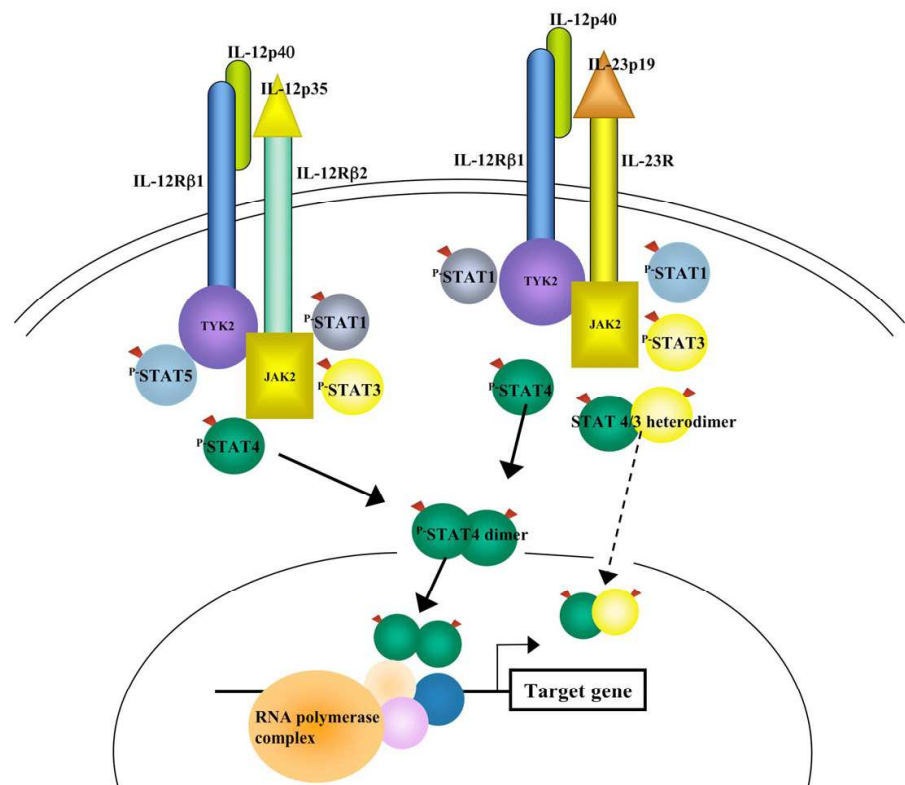
Fig. 2. Stat4 activation is a common feature of IL-23 and IL-12 signal-transduction pathways. IL-23 signal transduction is very similar to that of IL-12, they both use IL-12Rβ1, Jak2, Tyk2, Stat1, Stat3, Stat4, and Stat5. This common feature may explain similarities in TH1 function among IL-12 and IL-23.
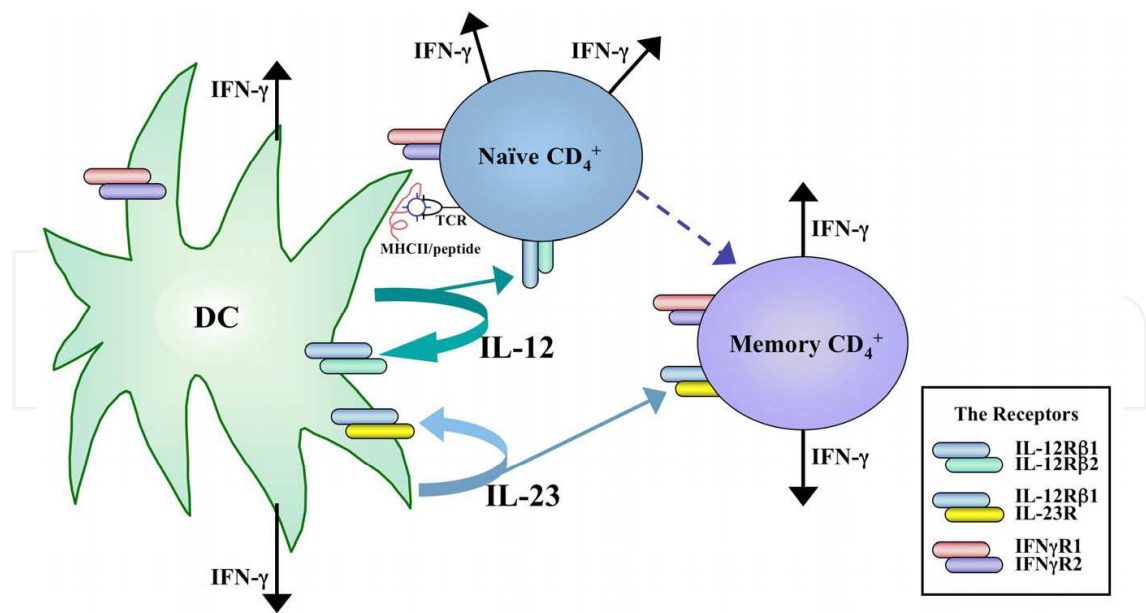

Fig. 3. IL-23 acts on memory CD4+ T cells and DC. IL-23 stimulation leads to IFN-γ production and proliferative response in memory but not naive CD4+ T cells. IL-23 differs from IL-12, which acts on naive cells but has negligible effects on murine memory cells. IL-23 and IL-12 share a similar function in promoting TH1 costimulation by inducing IL-12 and IFN-γ production by DC. MHCII, major histocompatibility complex class II.

tumor models, causing regression of established tumors (Brunda et al., 1993, Nastala et al., 1994, Cua et al., 2003) and inhibiting the formation of experimental metastases (Brunda et al., 1993, Nastala et al., 1994) and spontaneous metastases (Murphy et al., 2003, Becher et al., 2003). On the other hand, it has recently been reported that genetic deletion or antibody-mediated elimination of IL-23 in mice leads to increased infiltration of cytotoxic T cells into the transformed tissue, rendering a protective effect against chemically-induced carcinogenesis (Langowski et al., 2006). So far, it has been reported that expression of IL-23 and its receptors is detectable in activated macrophages, DCs, and keratinocytes in healthy skin (Piskin et al., 2006). We have previously reported that IL-23 is a potent and specific promoter of nuclear factor-kappaB (NF-κB) activation in HOSCC cells, *in vitro* and *in vivo* (Fukuda et al., 2010). Finally, we noted that IL-23 was secreted not only by DCs and macrophages, as shown in previous studies (Sospedra et al., 2005), but also by autologous cancer cells. Consequently, we consider the existence of an autocrine mechanism, in which tumor growth is promoted by IL-23 produced by autologous cancer cells. From these combined data, we believe that IL-23 plays a significant role in the growth and proliferation of oral cancer. Thus, IL-23 could be used as a predictor of poor prognosis in patients with oral cancer, and its antibody might be able to use as an inhibitor of oral cancer progression. Identification of the signaling pathways underlying these events might provide the key to elucidating the mechanism of development of oral cancer. Further investigations into the role of IL-23 will be required to fully understand IL-23-mediated tumor proliferation and to establish an IL-23-based oral cancer therapeutic strategy.

3.3 Vascular Endothelial Growth Factor (VEGF)

Oral cancer is an important cause of worldwide morbidity and mortality, with substantial economic, physiological, and psychosocial impacts due to its treatment modality and a great risk for recurrences and second primary OSCC development. Therefore, it is very important to understand the underlying cell biology of such tumors. It is now a well-accepted fact that angiogenesis is essential for the growth and metastasis of solid tumors, including oral squamous cell carcinoma. The main factor responsible for angiogenesis is VEGF and its receptors. The expression of VEGF protein has been found in a wide variety of cancer tissues, including human prostate cancer, head and neck squamous cell carcinomas, skin squamous cell carcinomas, gastric adenocarcinomas, and lung cancer cells (Weidne et al., 1993, Gasparini et al., 1993, Srivastava et al., 1998, Maeda et al., 1996, Kajita et al., 2001). It has also been shown that VEGF influences the differentiation, maturation, and function of DCs as an immunosuppressive cytokine (Gabrilovich et al., 1996, Banchereau et al., 1998). Interestingly, dendritic cells found in neoplastic infiltrates are frequently immature and defective in T-cell stimulatory capacity. It has been demonstrated that VEGFRs are also present on tumor cells themselves and other cells from the tumor microenvironment, in addition to tumoral endothelial cells (ECs) (Fukuda et al., 2010).

Therefore between these cells take place numerous and different interactions mediated via paracrine/autocrine pathways that promote angiogenesis, uncontrolled tumor proliferation and metastasis. In consequence, estimation of VEGF expression and its receptors became a reliable prognostic tool in OSCCS, predicting the poor disease-free survival, poor overall survival, and metastatic disease.

Furthermore, Saito et al. (1998, 1999) reported that the expression of VEGF is inversely related to the density of DCs in gastric adenocarcinoma tissue. In our study, it was found

that VEGF in the primary oral tumor is expressed more strongly in PN+ cases than in PN-cases, thus demonstrating that VEGF is associated with the metastasis to RLNs in oral cancer. We also found that in oral cancer the expression of VEGF is inversely related to the density of S-100+ and CD1a+ DCs, although it is also positively correlated with the density of CD83+ DCs (Kusama et al., 2005). Understanding the distribution and role of VEGF and its receptors in the progression of OSCC will be essential to the development and design of new therapeutic strategies.

4. Role of transcriptional factors in tumor microenvironment

The ancient stress response is the innate immune response, regulated by several transcription factors, among which NF-kappaB plays a central role. The hypoxic response is also ancient stress response triggered by low ambient oxygen (O_2) and controlled by hypoxia inducible transcription factor-1, whose a subunit is rapidly degraded under normoxia but stabilized when O_2-dependent prolylhydroxylases (PHDs) that target its O_2-dependent degradation domain are inhibited. Thus, the amount of HIF-1alpha, which controls genes involved in energy metabolism and angiogenesis, is regulated post-translationally. So, NF-kappaB and hypoxia-inducible factor-1 were selected as the typical transcriptional factors in this section.

4.1 Nuclear Factor (NF)-kappaB

Transcription factor NF-κB has key roles in inflammation, immune response, tumorigenesis and protection against apoptosis (Li et al., 2002, Karin et al., 2002, Orlowski et al., 2002). In most cells, NF-κB is kept inactive in the cytoplasm as a heterodimeric complex composed of p50 and p65 (RelA) subunits bound to the inhibitory protein, inhibitor of κB (IκBα) (Baeuerle et al., 1988, Baeuerle et al., 1989, Haskill et al., 1991). Insight into the signaling mechanisms that lead to IκBα phosphorylation have identified a high-molecular weight protein complex known collectively as the IκB kinase (IKK) signalosome and including IKKα, IKKβ and IKKγ also known as NF-κB essential modulator (NEMO) (Karin, 1999, Mercurio et al., 1997). IKKα and IKKβ have been identified as catalytic subunits, whereas IKKγ is a regulatory subunit (Karin, 1999, May et al., 1999). Generally, after stimulation by various reagents, IκBα is phosphorylated at serine residues 32 and 36 by IKKα and IKKβ, together with the scaffold protein NEMO/IKKγ (Karin, 1999). Serine phosphorylation results in polyubiquitination of IκB and its subsequent degradation by the proteasome, allowing NF-κB to translocate to the nucleus and activate its target gene (Karin et al., 2002, Karin, 1999, Smahi et al., 2002).

4.2 Hypoxia Inducible Factor (HIF)-1alpha

Protection against hypoxia in solid tumors is an important step in tumor development and progression. One system in hypoxia protection of tumor cells is represented by the hypoxia-inducible factor 1 (HIF-1) system which plays a crucial role in biologic processes under hypoxic conditions, especially in angiogenesis and carcinogenesis (Maxwell et al., 1997, Ryan et al., 1998).

HIF-1 is a heterodimer, composed of HIF-1α (120 kDa) and HIF-1β (91, 93, 94 kDa) (Wang et al., 1995). HIF-1α subunit, is a transcription factor in response to cellular hypoxia, plays an

important role in tumor growth and metastasis by regulating energy metabolism and inducing angiogenesis (Seagroves et al., 2001). However, under normoxic conditions, HIF-1α is maintained at low levels due to continuous degradation via the ubiquitin-dependent proteosome pathway, and this pathway is inhibited by hypoxia and by p53 or von Hippel-Lindau tumor-suppressor gene defects, leading to stabilization of the HIF-1α protein (Huang et al., 1996, Ravi et al., 2000, Maxwell et al., 1999, Stroka et al., 2001). Therefore, hypoxia can lead to a rapid increase in HIF-1α protein levels (Huang et al., 1996, Stroka et al., 2001, Wang et al., 1993, Wang et al., 1995). Furthermore, HIF-1α up-regulates a number of important factors for tumor expansion, including VEGF, a key factor in tumor angiogenesis (Akakura et al., 2001, Carmeliet et al., 1998, An et al., 1998). In several cancers, overexpression of HIF-1α protein has been found to be associated with tumor aggressiveness and with an unfavorable prognosis (Maxwell et al., 1997, Birner et al., 2000, Kuwai et al., 2003). Hypoxia has also been reported to induce wild-type p53 via a different pathway than DNA-damaging agents (Graeber et al., 1994). The hypoxic/anoxic induction of p53 selects for tumor cells that lack functional p53, and hence evidence diminished apoptotic potential (Graeber et al., 1996). Elevated levels of HIF-1α are noted in various malignant tumors (Maxwell et al., 1997), but it is unclear whether this is so in oral carcinoma. Therefore, we have examined the implications of HIF-1α expression in HOSCC, *in vitro* and *in vivo*. NanoCulture plate system was used to duplicate hypoxic condition within tumor mass of living organisms by the three-dimensional cell culture. As the results, we found that HIF-1α regulates the expression of VEGF, and that HIF-1α may be regulated by p53 in SCC of the oral cavity (Fukuda et al., 2010).

4.3 p53

The p53 gene is a highly characterized tumor suppressor that encodes a protein with a molecular weight of 53 kilo Daltons. The p53 gene is also known as a transcription factor that can arrest the cell cycle at the late G1 phase in cells with sub-lethal damage in their genome until their complete repair, or induce apoptosis in cases of irreparable injury, and further activate the transcription of specific genes (El-Deiry et al., 1992, Cordon-Cardo, 1995). Hence, among the genetic changes involved, inactivation of the *p53* tumor suppressor gene by point mutation and allele loss is considered to be the most common event underlying malignancies of every organ (Hollstein et al., 1991). These alterations also seem to be related to the multi-step processes of oral carcinogenesis (Crosthwaite et al., 1996, Stoll et al., 1998). Mutations of *p53* must occur during early stages in the development of head and neck SCCs because they are already present in premalignant lesions (Shin et al., 1994). Mutations of *p53* gene are not necessarily the critical, sole, nor the consistent culprit in oral SCCs patients, however, between 30% and 50% of SCCs of this region have been reported to harbor *p53* gene alterations (Somers et al., 1992, Caamano et al., 1993, Nylander et al., 2000). By contrast, other markers are less suitable due to their lack of stability, variability, or difficulties with technical requirements for their detection. The genes that occur high frequent alterations more than *p53* have not been found so far. Furthermore, it has been described that cancer with the mutated *p53* gene is resistant to radio-/chemotherapy and the patient has poor prognosis than cancer patient with the wild-type *p53* gene (Obata et al., 2000). Therefore, analysis of mutations in this particular gene gives a good indication of clonal expansion of malignancies and important prognostic information. Because the wild-type form of p53 has a half-life of only 6 to 30 minutes, the protein cannot be generally detected by immunohistochemistry; however, if the DNA is damaged, p53 protein accumulates and

NO.	Age	Gender	Locaion	Differentiation	pTNM	Stage	immunohistochemistry p53	p53 gene alteration
1	87	M	Oral floor	well	T2N2bM0	IVA	+	Exon 7 codon 258: GAA →CAA Glu →Gln
2	48	F	Gingiva	well	T4N0M0	IVA	—	—
3	56	F	Buccal mucosa	well	T2N0M0	II	—	—
4	75	M	Tongue	well	T4N2cM0	IVA	+	Exon 7 codon 244: GGC →GGA (silent)
5	55	M	Oral floor	well	T2N0M0	II	—	—
6	54	M	Tongue	well	T4N2bM0	IVA	—	—
7	54	M	Oral floor	well	T2N2aM0	IVA	+	—
8	70	M	Tongue	well	T2N0M0	II	—	Sequencing failed
9	67	M	Maxillary gingiva	well	T4N3M0	IVB	4+	Exon 5 codon 151: CCC →CCA (silent)
10	92	M	Soft palate	well	T2N0M0	II	+	Sequencing failed
11	66	M	Tongue	well	T2N0M0	II	+	Exon 7 codon 244: GGC →AGC Gly →Ser
12	87	M	Tongue	well	T2N0M0	II	+	Exon 5 codon 154: 1 bp insertion (Frameshift)
13	48	F	Tongue	well	T1N0M0	I	+	—
14	85	M	Tongue	well	T2N1M0	III	—	—
15	56	F	Tongue	well	T1N2bM0	IVA	—	—
16	67	M	Mandibular gingiva	well	T1N2bM0	IVA	+	Sequencing failed
17	55	M	Tongue	well	T1N0M0	I	—	—
18	85	M	Buccal mucosa	well	T1N0M0	I	+	—
19	50	M	Mandibular gingiva	well	T3N1M0	III	—	—
20	67	M	Mandibular gingiva	well	T4N0M0	IVA	+	—
21	79	M	Buccal mucosa	well	T2N0M0	II	+	—
22	54	M	Buccal mucosa	well	T1N0M0	I	—	Exon 8 codon 282: C(T)GG (insertion) (Arg →Trp)
23	54	M	Mandibular gingiva	well	T4N1M0	IVA	+	Not amplified
24	62	M	Mandibular gingiva	well	T1N0M0	I	—	Exon 8 codon 274: G(C)TT (insertion) (Val →Leu)
25	60	M	Maxillary gingiva	well	T1N0M0	I	+	—
26	79	M	Mandibular gingiva	moderately	T4N2cM0	IVA	4+	—
27	85	F	Tongue	moderately	T2N1M0	III	—	Not amplified
28	54	M	Tongue	moderately	T1N0M0	I	+	—
29	54	M	Tongue	moderately	T4N2bM0	IVA	—	Exon 8 codon 282: CGG →CGC (silent)
30	75	M	Mandibular gingiva	moderately	T1N0M0	I	+	—
31	66	F	Mandibular gingiva	moderately	T1N0M0	I	4+	—
32	65	M	Mandibular gingiva	moderately	T2N0M0	II	—	Exon 8 codon 274: GTT ◇ GCT Val →Ala
33	88	M	Mandibular gingiva	moderately	T2N0M0	II	—	Exon 8 codon 282: CGG →CGC (silent)
34	79	M	Mandibular gingiva	moderately	T2N0M0	II	+	Exon 6 codon 222: CCG →CCA (silent)
35	54	M	Buccal mucosa	moderately	T2N0M0	II	—	Exon 8 codon 274: GTT →CTT Val →Leu
36	64	M	Buccal mucosa	poorly	T2N0M0	II	4+	Sequencing failed
37	62	M	Tongue	poorly	T2N1M0	III	+	Exon 8 codon 274: GTT →CTT Val →Leu
38	60	M	Tongue	poorly	T2N1M0	III	—	—
39	60	M	Tongue	poorly	T1N0M0	I	+	Exon 8 codon 273: CGT →CCT Arg →Pro
40	68	M	Maxillary gingiva	poorly	T3N0M0	III	—	Not amplified

p53 gene alteration: 14/33 cases (42.4%)

Table 1. The correlations between p53 expression, p53 gene alteration and clinicopathological variables in 40 cases of oral squamous cell carcinomas.

becomes detectable (Langdon et al., 1992). So, to assess the frequency of *p53* mutations in HOSCCs and the correlations between p53 immunohistochemical detections and *p53* gene alterations, we examined them by use of the formalin-fixed, paraffin-embedded specimens from 40 patients with oral SCC treated in the Department of Oral and Maxillofacial Surgery, Meikai University Hospital, Saitama, Japan, from 1970 to 2001. Diagnosis of oral lesions was based on histological examination of hematoxylin and eosin-stained slides. Of the 40 SCC patients, there were 34 men and 6 women, whose ages ranged from 48 to 92 years, with a mean age of 66.2 years. A majority of the patients were over 50 years of age. All specimens were obtained from surgical biopsies that no patients had undergone chemotherapy or radiotherapy preoperatively. As the results of immunohistochemistry using MAb p53 antibody, 22 of 40 cases (55%) were positive. Then the alterations in exons 5 to exon 8 of the *p53* gene were analyzed by PCR-SSCP and direct sequencing. The *p53* point mutations were detected in 14 of 33 cases (42.4 %) **(Table 1)**. However, it had no correlations between p53 immunoreactivity, the detection of *p53* gene alterations and clinico-pathological variables. These findings support those of previous reports (Kärjä et al., 1997).

It has recently been reported that in combination with an overexpression of p53 protein, HIF-1α protein overexpression tends to indicate a dismal prognosis (Sumiyoshi et al., 2006). In addition, it has also described that p53 inhibits expression of the p65 subunit of NF-κB and its gene product Bcl-2 (Amin et al., 2009). For these reasons, it has been suggested that there is close relationship between p53 and tumor microenvironment.

5. Conclusions

The efficient elimination of cancer cells via immunodefense mechanisms remains the most ideal therapy. However, it is important to recognize that the dysfunctional immune state that exists in cancer patients will result in a poor response to vaccination procedures. Therefore, in order to enable an immunotherapy challenge, it is necessary to restore the increased levels of immunosuppressive factors, such as IL-10, IL-23, RCAS1, VEGF and/or TGF-β1, in the tumor microenvironment of cancer patients to normal levels. In addition, whether DCs function normally and efficiently remains an important key for the induction of anticancer immunity.

Further investigation will be required to establish a strategy of basic molecular-mechanism-based and clinical studies to determine the most effective oral cancer therapy, which should be tailor-made for the individual patient.

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Tumor Microenvironment and Myelomonocytic Cells

Edited by Dr. Subhra Biswas

Tumor microenvironment represents an extremely dynamic niche shaped by the interplay of different cell types (e.g. tumor cells, stromal cells), their soluble products (e.g.cytokines, chemokines and growth factors) and varied physico-chemical conditions (e.g low oxygen concentration or hypoxia). Recent studies have identified myelomonocytic cells as key players in regulating the tumor microenvironment and hence, tumor progression in a variety of cancers. In view of these findings, the present book attemps to provide a comprehensive account of the diversity of tumor microenvironment across different cancers and how myelomonocytic cells have taken the center-stage in regulating this niche to direct cancer progression. A better understanding of the myelomonocytic cells and the mechanisms by which they regulate cancer progression will open new vistas in cancer therapeutics.

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