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Review

Main Molecular Markers of Oral Squamous Cell Carcinoma

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Abstract

Oral squamous cell carcinoma (OSCC) represents a worldwide problem, with a poor prognosis. Despite advances in the OSCC therapy, it remains as a disease of later diagnosis and high level of recurrence, what deeply implicates in the life quality. Therefore, it is necessary to define molecular markers to allow early diagnosis, and to identify new therapeutic targets. In this review, we have collected scientific data on main OSCC biomarkers that have been published since 2004. They were classified into different categories, according to their main role: cell proliferation/cell cycle regulators, apoptosis, angiogenesis, and cellular adhesion/metastasis.

Keywords: Mouth Neoplasms; Squamous cell carcinoma; Biological markers; Prognosis.

Introduction

Squamous cell carcinoma (SCC) is the most common cancer of the oral cavity encompassing 90% of all oral malignancies, with about 300 000 new annual cases worldwide.[1-3] It is estimated that there were 35 310 new cases of oral cavity and pharynx cancer (25 310 men and 10 000 women), and 7 590 people died of this disease in the United States, in 2008.4 OSCC is an aggressive malignant cancer, with high mortality and morbidity, which commonly occurs in male middle-aged and older individuals.[2] Noteworthy, this kind of cancer has been strongly correlated with specific risk factors, such as tobacco and/or alcohol use.[2,4-5] In spite of the therapeutic advances, the 5-year survival time remains in about 55%.[6]

Several molecular markers implicated in the carcinogenesis of OSCC have been evaluated by many investigators, including molecules involved in the cell cycle regulation, apoptosis, angiogenesis, DNA repair system and degradation of extracellular matrix. Identifying these molecules by analysis of DNA, RNA and protein expression might permit the early diagnosis, beyond to predict better therapeutic alternatives. The most used techniques have been cDNA microarray, PCR, in situ hybridization, immunohistochemistry (IHC), ELISA and western-blot, among others. However, the available evidence about the molecular markers still remains inconclusive. Accordingly, there is a continuous needing to define the most important biological markers for OSCC progression and invasiveness. The aim of the present review article is to outline the current knowledge on the role of some tumor biological markers in carcinogenesis of OSCC, by reviewing the last years of research in this field. Attempts were made to point out the most studied molecular markers of OSCC.

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The Mechanisms of Carcinogenesis

Carcinogenesis is the process by which normal cells undergo malignant transformation, following several genetic and epigenetic alterations. The cancer starts when the cells present uncontrolled proliferation.[7] Cell division is a physiological process that occurs in almost all tissues and under many circumstances. The balance between proliferation and programmed cell death (apoptosis) is kept by tightly regulation between both processes. The transition of normal epithelium to invasive cancer is progressive and accompanied by "multiple hits" which promote proliferation, angiogenesis, local invasion and, eventually, distant metastasis.[8] The malignant process involves DNA damage, leading to changes of the production and/or function of certain proteins. These changes may occur by failures during the replication of DNA, or by deficiencies of its repair engine. DNA alterations responsible for cancer usually occur in genes that regulate the cell cycle, growth and differentiation, which are classified into oncogenes and tumor suppression genes. The oncogenes are originated from proto-oncogenes; these latter genes are involved in basic mechanisms of normal cell growth regulation and include growth factors, receptors for growth factors, signal transducers and nuclear transcription factors.[7] Most of the oncogenes implicated in other cancer types also contribute to OSCC.[8]

Tumor suppressor genes encode proteins that normally block the uncontrolled cell proliferation that leads to cancer.[7] These genes are usually involved in the regulation of discrete check-points during cell cycle progression, DNA replication, and mitosis. Cellular stress and a variety of insults can activate tumor suppressor pathways to arrest the cell cycle. The initial alterations in OSCC seem to occur at the basal cell layer by the influence of smoke, alcohol and/or other carcinogens, and may involve deactivation of key tumor suppressors.[8]

Main Biological Markers of Oral SCC

The activation of receptors by growth factors is known to induce different cellular events.[8] ErbB (also known as HER) is a family of proto-oncogenes that codify tyrosine kinase growth factor receptors, which are involved in cell proliferation and differentiation. This family includes the epidermal growth factor receptor (EGFR, HER1 or ErbB-1), ErbB-2 (HER-2 or neu), ErbB-3 (HER-3) and ErbB-4 (HER-4), and their over-expression may contribute to the tumoral progression.[9-10] The EGFR is a transmembrane glycoprotein with several extracellular ligands, including EGF.8,[11] Importantly, ErbB-1 and ErbB-2 have been found over-expressed in OSCC (Table1).[12-15]

Pro-cancer signals are controlled by the expression and transcription of oncogenes, by means of an interaction between transcriptional machinery (RNA polymerase II and transcription factors) and transcriptional regulatory components (promoter elements, enhancers, silencers and locus control regions). Among the transcription factors, c-Myc and AP-1 (a dimmer comprised by c-Jun and c-Fos) seem to have a great relevance for cancer progression[16], being commonly expressed in OSCC (Table 1).[17-19] They are also implicated in angiogenesis and metastasis, as well as self-sufficiency of growth signals.[16]

Proliferating cell nuclear antigen (PCNA) is a nuclear protein that appears in the nucleus during the late G1 phase, and increases during the S phase to work as an accessory protein for DNA polymerase, declining during the G2 and M phases. It plays a key role in cell proliferation, DNA repair and cell-cycle control.[20-21] Ki67 is another protein involved in cell proliferation, which is overexpressed at initial stages of oral carcinogenesis. It is detected in the cell nucleus in the G1, S, G2 cell cycle phases and mitosis, being absent in the G0 phase.[22-24] Functional alterations in PCNA and Ki67 activities are common genetic events in various types of cancer, being an important proliferation marker in OSCC (Table 1).[20-21,25-33]

Cyclins are a group of cell cycle regulatory proteins, which are inactive during the G0 phase. The formation of the cyclin/cyclin-dependent kinases (C/CDKs) complex stimulates cell mitosis.[7,34] The Cyclin D1 regulates the progression of a cell through the G1 phase. Its over-expression plays an essential role in the transition between G1 and S phase in proliferating cells.[35-36] Recent studies demonstrate that striking expression of cyclin D is a common feature of OSCC (table1).[19,36-39]

pRb is a nuclear phosphoprotein hypothesized to normally act as an inhibitor of cell proliferation. p16 is an inhibitor of cyclin dependent kinases, repressing the transcription of S phase genes. The loss of p16 function allows cyclin D1 to catalyze the phosphorylation of pRb, triggering uncontrolled proliferation.[36,40-42] p16 and pRb are genes commonly inactivated in various cancers, and overexpressed in OSCC (Table1).[42-45]

Table 1 - Cell proliferation /cell cycle regulators markers

N	Marker	Method	End point	Reference
59	EGFR	Elisa	Overexpressed in 57.6%.	Chen et al.[12]
129	EGFR	IHC	Overexpressed in 42.6%.	Schartinger et al.[81]
19	EGFR	IHC	Higher expression than normal tissue.	Ekberg et al.[24]
109	EGFR	IHC	Overexpressed in 73.42%.	Laimer et al.[50]
47	EGFR	IHC	Overexpressed in 74.5%.	Diniz-Freitas et al.[21]
59	ErbB-2	Elisa	Overexpressed in 40.6%.	Chen et al.[12]
70	ErbB-2	IHC	Significant risk predictor for OSCC progression.	Freier et al.[33]
62	ErbB-2	IHC	Expression significantly associated with a poor prognosis.	Silva et al.[88]
154	ErbB-2	IHC	Membrane expression was found in 13%.	Weed et al.[108]
61	ErbB-2	IHC	Intermediate to high positivity 49.2% of the cases.	Chen et al.[11]
129	ErbB-2	IHC	Overexpression in 3.1%.	Schartinger et al.[81]
19	ErbB-2	IHC	Same expression in tumors, metastasis and normal tissue.	Ekberg et al.[24]
54	ErbB-2	IHC	Membrane positivity in 83.3%; cytoplasmic positivity in 42.6%.	Aguiar et al.[14]
30	ErbB-2	IHC	Positivity in 50%.	Fong et al.[29]
40	ErbB-2	IHC	Positivity in 75%.	Angiero et al.[3]
19	ErbB-3	IHC	No overexpression.	Ekberg et al.[24]
19	ErbB-4	IHC	No overexpression.	Ekberg et al.[24]
70	c-myc	IHC	Significant risk predictor for OSCC progression.	Shah et al.[84]
24	c-jun	IHC	Positivity in 87.5%.	Turatti et al.[102]
70	c-jun	IHC	Phosphorylated c-Jun positivity in 60%.	Kuo et al.[46]
24	c-fos	IHC	Positivity in 79.1%.	Turatti et al.[102]
112	PCNA	IHC	Overexpressed in older patients.	Siriwardena et al.[90]
20	PCNA	IHC	Higher expression in OSCC than in oral dysplasia sequence.	Lee et al.[51]
113	PCNA	IHC	Overexpressed in the tumours with lymph node metastasis.	Myoung et al.[66]
46	Ki67	IHC	Overexpressed in poorly histological differentiated carcinomas.	Kodani et al.[44]
60	Ki67	IHC	Higher expression in invasive front than in the center of the tumor.	Dissanayake et al.[22]
62	Ki67	IHC	Higher expression in patients with shorter survival time.	Silva et al.[88]
19	Ki67	IHC	Higher expression in OSCC than in oral dysplasia sequence.	Iamaroon et al.[40]
47	Ki67	IHC	Strong nuclear positivity in 85%.	Esguerra et al.[25]
10	Ki67	IHC	Strong staining in all cases.	Farrar et al.[26]
47	Ki67	IHC	Higher positivity in the invasive tumor front.	Tumuluri et al.[101]
39	Ki67	IHC	Positivity in up to 60% of neoplasic cells.	Foschini et al.[31]
50	Ki67	IHC	Higher expression in OSCC than in oral dysplasia sequence.	Shibata et al.[85]
23	Ki67	IHC	Overexpressed.	Teresa et al.[96]
81	Ki67	IHC	Overexpressed in 70.4%/44.4% in early/no local recurrence.	Aguiar et al.[14]
113	Ki67	IHC	Overexpressed in patients with worst prognosis.	Myoung et al.[66]
55	Cyclin D1	IHC	Overexpressed in 31% of areca-using patients.	Liu et al.[54]
241	Cyclin D1	IHC	Overexpressed.	Sathyan et al.[80]
24	Cyclin D1	IHC	Up-regulated.	Turatti et al.[102]
33	Cyclin D1	IHC	High labeling indices have been significantly related to a poor outcome.	Thomson et al.[97]
45	Cyclin D1	IHC	Expression was not related to cervical metastasis.	Maahs et al.[60]
40	Cyclin B1	IHC	Overexpression related to mitosis and metastasis.	Harada et al,[38]

32	Cyclin B1	IHC	Positivity in 80% of cases.	Pannone et al.[73]
55	Rb	IHC	Positivity in 70% of areca users.	Liu et al.[54]
220	Rb	IHC	Altered expression in 90%.	Soni et al.[92]
45	Rb	IHC	Overexpression in 87% patients.	Muirhead et al.[65]
241	p16	IHC	Downregulation was correlated with shorter disease free survival.	Sathyan et al.[80]
66	p16	IHC/FISH	Expression was correlated with worst biological behavior.	Suzuki et al.[94]
45	p16	IHC	Overexpression in 13%.	Muirhead et al.[65]

Apoptosis Control

The imbalance of apoptotic pathways contributes to immortality of replicating cells, supporting the accumulation of sequential genetic alterations that would normally induce cell death.[55] Bcl-2 is a proto-oncogene that serves as a primary regulator of cell cycle, which is known to modulate apoptosis, protecting against cell death. The Bcl-2 protein has been shown to form heterodimers with Bax, a pro-apoptotic protein that is expressed selectively during apoptosis.[56] The apparent relative ratio Bcl-2/Bax has been suggested as a critical determinant of cell survival in OSCC [57] (Table 2).

Genetic alterations involving the tumor suppressor gene p53 are frequently observed in head and neck SCC. Inactivation of these genes appears to be involved in the early stages of the disease.[8,57] Relevantly, p53 inhibits the expression of Bcl-2 and promotes the synthesis of Bax, thus contributing to programmed cell death7. In this context, mutations of the p53 gene and the overexpression of its protein are present in about 50% of OSCCs[58-59] (Table 2).

p63 is a member of the p53 family that plays a critical role in epithelial tumor formation.[60] p63 gene encodes a series of protein isoforms that are able to promote or repress p53-related functions.[61] Besides

Table 2 - Apoptosis control markers

N	Marker	Method	End point	Reference
66	Bcl-2	IHC	Expressed in 54.5%. Lack of expression is a hallmark of aggressive behavior.	Lo Muzio et al.[57]
81	Bcl-2	IHC	Overexpressed in 13.6%/16.7% in early/no local recurrence.	Aguiar et al.[14]
56	Bcl-2/Bax	IHC	Better prognosis when negative/positive expression, respectively.	Kato et al.[43]
46	p53	IHC	No correlation with prognosis.	Kodani et al.[44]
19	p53	IHC	Higher expression in dysplasia-carcinoma sequence.	Iamaroon et al.[40]
60	p53	IHC	Weak predictor of malignancy progression.	Farrar et al.[26]
55	p53	IHC	Expressed in 81% of areca users.	Liu et al.[54]
52	p53	IHC	Expression correlated with angiogenesis.	Abbas et al.[1]
106	p53	IHC	Overexpression associated with metastasis and poor outcome.	Oliveira et al.[15]
27	p53	IHC	Positivity in 55.6%/63% of early/no recurrence.	Aguiar et al.[14]
21	p53	IHC	Detected in both central and peripheral regions.	Abbas et al.[1]
39	p63	IHC/PCR	No relationship with prognosis.	Foschini et al.[31]
106	p63	IHC	Decreased intensity associated with poor outcame.	Oliveira et al.[15]
26	p63	IHC	Nuclear immunoreativity detected in all cases of betel users.	Haniffa et al.[37]
36	p63	WB/IHC/	Expressed in all tumors and matched normal tissue.	Sniezek et al.[91]
22	p63	RT-PCR	Expressed in OSCC and dysplasias.	Bortoluzzi et al.[9]
46	p21	IHC	No correlation with histological differentiation and mode of invasion.	Kodani et al.[44]
106	p21	IHC	Overexpression in 61.3%.	Nemes et al.[69]
16	Survivin	IHC	Positivity in 100% of the cases.	Lo Muzio et al.[58]
96	Survivin	IHC	Positivity in 98% of cases.	Lin et al.[52]
296	Survivin	FISH/IHC	High expression in 67.3%.	Freier et al.[34]
32	Survivin	IHC	Expressed during early and late phase of oral carcinogenesis.	Pannone et al.[73]

p63, there is another related protein named p73, that may be associated with the early events in human oral carcinogenesis, and with the nodal status of patients with oral carcinoma, being a possible indicator for malignant transformation of oral epithelial dysplasia[62] (Table 2).

p21 was initially identified as a cell cycle arrest protein. It is induced by both p53-dependent and p53-independent mechanisms. As an inhibitor of cell proliferation, p21 (WAF1/Cip1) plays an important role in tumor suppression. Nevertheless, p21 can assume both pro- or anti-apoptotic functions in response to anti-tumor agents depending on cell type and cellular context,[63] and it can be found upregulated in OSCC75 (Table2).

Survivin, or TIAP, is a member of the Inhibitor of Apoptosis Protein (IAP) family that also plays a role during mitosis;[64-65] it is expressed in several tumors and tissues with proliferating cells, including OSCC.[66] Most IAP members inhibit apoptosis by binding to effector caspases[67-68] (Table2).

Molecules Implicated in Angiogenesis

Angiogenesis is a pivotal step in tumor growth, progression and metastasis, which is a process controlled by a variety of factors. Among them, vascular endothelial growth factor (VEGF) overexpression has been shown to be associated with angiogenic phenotypes and a poor prognostic in oral cancer[78] Thus, the strong expression of VEGF in OSCC would require a more radical therapeutic intervention, especially for the early stage cases.[79] In fact, it has been well established that VEGF promotes the progression of OSCC by up-regulating microvessel density.[8] VEGF has been regarded as the most likely candidate for the induction of angiogenesis in tumor growth, because it is a soluble endothelial cell mitogen, and its receptors are selectively expressed in the endothelium. A major difficulty to study angiogenesis in humans is the lack of direct methods for measuring the density of the microvasculature in histological sections of the tumor, and whether this measurement represents the angiogenic status of the tumor.[80] The expression of VEGF-C in OSCC triggers lymphatic angiogenesis, which may result in a higher risk of cervical lymph node metastasis. The angiogenetic effects of VEGF-C may also favour the onset of late lymphatic and haematogeneous metastases.[81] Uheara et al.[79] showed that expression of VEGF in OSCC may be of great value in assessing its prognosis, and would provide important clues to programming treatment (Table3).

Integrins are transmembrane glycoprotein adhesion molecules that mediate cell-ECM and cell-cell adhesive interactions. Recent evidence has suggested an important role for integrins in blood vessel formation, and also in the regulation of tumor angiogenesis. Some integrin blockers are under Phase I and II clinical trials for treating several types of cancer.[82] Furthermore, integrins seem to be linked to the regulation of mitotic machinery, what has important implications in cancer. The mechanisms by wich integrins modulate these events have just beginning to be unraveled.[83] Increased expression of the integrin-α3 gene was associated with lymph node metastasis in OSCC; it is a major receptor for laminin-5 in basement membrane. Integrin-$\alpha 3\beta 1$ is also expressed at high levels in most adherent transformed cells, and it could have similar roles in extracellular matrix remodeling during tumorigenesis and cell invasion. Therefore,

Table 3 - Angiogenesis markers

N	Marker	Method	End point	Reference
220	VEGF	IHC	Increased expression was the most adverse prognostic factor.	Arora et al[1,4]
63	VEGF	IHC	High expression requires more radical treatment.	Uehara et al.[104]
51	VEGF	IHC	Higher expression in T2 than in T1 tumors.	Schimming et al.[82]
50	VEGF/ VEGF-C	IHC	VEGF-C expression was down-regulated in the deep area of tumor tissue; VEGF was up-regulated throughout the tumor tissue.	Ohno et al.[72]
20	VEGF-C	IHC	High expression was correlated with advanced tumor status.	Miyahara et al.[64]
87	VEGF-C	IHC	No correlation with lymph node metastasis/histopathological grade.	Faustino et al.[27]
28	VEGF-C	IHC	Expression was significantly correlated with poor outcome.	Sedivy et al.[83]
15	Intergin-α3	Microarray	Its expression was correlated with cervical lymph node metastasis	Nagata et al.[68]
66	Integrins α3/ β4/β5	RT-PCR	Their expression was correlated with cervical lymph node metastasis and poor outcome.	Kurokawa et al.[47]

integrin-α3 expression is an important biomarker for lymph node metastasis in OSCC [84] (Table 3).

Cellular Adhesion/Metastasis

The development of malignant epithelial cancer is associated with disruption of cell-to-cell and cell-to-matrix adhesion.[90] Syndecans are a family of closely related proteins (syndecan-1−4) encoded by four different genes, that interact with extracellular matrix components, with other cell surface components, or even with growth factors. Syndecan-1 is the most studied member, known to regulate cell adhesion, migration and differentiation. It binds cells via its heparan sulfate chains to a variety of components of the interstitial matrix. It has been found to be down-regulated in OSCC[90-91] (Table4).

Intercellular adhesiveness is mediated by a family of glycoproteins named cadherins. They are composed by an extra-cellular domain, involved in Ca++-dependent homophilic binding to adjacent cells, a trans-membrane domain, and an intra-cellular domain which binds to proteins called catenins.[92-93] In epithelial cells, the adhesiveness is mediated by epithelial-cadherin (E-cad), localized mainly in the zonula adherens junctions. The cadherin family also includes other members: neural-cadherin (N-cad) and placental cadherin (P-cad).[93] In particular, P-cad is a protein homologous to E-cad; whereas E-cad is involved in the adherens type of intercellular junctions of keratinocytes, P-cad is detected on the cell-cell contact surface of basal keratinocytes. The expression of P-cad in epithelial tissues appears to identify cell populations with proliferative activity, and its expression decreases as cells undergo differentiatiation.[94] Then, Lo Muzio et al.[94] pointed out that P-cad as an early marker of poor prognosis and abnormal or lack of P-cad expression could constitute a hallmark of aggressive behavior in OSCC (Table4).

The possible role exerted by cadherins in human carcinogenesis has been suggested by a number of studies. Alterations of cadherin expression are associated with the loss of cellular differentiation, the acquisition of an invasive phenotype, a poor prognosis in many types of cancer, and early local recurrence.[26,95] Down-regulation of E-cad was reported to be directly related to invasiveness and progression of many human epithelial tumours, including OSCC,[96] playing a critical role in cancer development and metastasis[95] (Table 4).

As mentioned before, catenins are intracellular proteins that link the cytoplasmic domains of cadherins to the cytoskeleton to promote its biological functions. α−catenin is involved in the regulation of actin cytoskeleton and cell-cell adhesion, which when perturbed could contribute to cancer progression. β−Catenin is a multifunctional adaptor protein involved in cadherin-mediated cell−cell adhesion and in responses to the activation of several signal transduction pathways. −Catenin is a cytoplasmic protein structurally and functionally related to β-catenin.[92] Both β- and y-catenins play a pivotal role in maintaining cellular polarity and serve as cell-cell attachment molecules, through direct interaction with the cytoplasmic domain of E-cad.[92,96] In addition to its role in E-cad-mediated cell adhesion, β-catenin is a transcription factor in the Wnt pathway, which promotes the transcription of genes involved in cellular proliferation and apoptosis inhibition.[96] Ueda et al. showed that tumors with absent or reduced expression of β- and −catenin have a significant association with poor prognosis in patients with OSCC and should be selected for more aggressive treatment[92] (Table4). Cytokeratins are polypeptide components of epithelial cell cytoskeleton that are expressed in various types of epithelia, in different combinations. Serum cytokeratin levels have been used as biological markers to characterize a wide variety of epithelial tumors, being correlated with a poor clinical prognosis of OSCC[97-98] (Table 4).

CD44 is an adhesion molecule that interacts with hyaluronic acid, suggesting a role in the regulation of cell substrate interactions, as well as cell migration.[99] In the normal epithelium, CD44 is expressed in the basal surface; however, in the epithelium with histologic dysplastic changes, CD44 expression reaches all the epithelium layers. Its overexpression is also observed in 90% of invasive HNSCC. CD44 undergoes interaction with other molecules, such as ErbB and matrix metalloproteinase (MMP) family. In addition, the transition from non-metastatic to metastatic tumors has been correlated with increased expression of CD44 antigen[100] and a poor outcome in OSSC [99,101] (Table 4).

MMPs are a family of zinc-dependent proteinases that can degrade all components of extracellular matrix. They are classified into four groups according to their substrate specificity: collagenases (MMP-1, -8 and -13), gelatinases (MMP-2 and 9), stromelysins (MMP-3, 10, and 11), and membrane-type MMPs (MMPS 14-17, 24 and 25). This family of endopeptidases is associated with exatracellular matrix degradation in physiological and pathological conditions such as tumor metastasis.[102] In OSSC, MMPs are correlated with poor prognosis [99,101,103-104] (Table 4).

Laminin, one of the main components of the basal membrane, is a glycoprotein with adhesion function. Tumor cells bind to laminin receptors on the basal

Table 4 - Cellular adhesion / metastasis markers

N	Marker	Method	End point	Reference
43	Syndecan-1	IHC	Down-regulated in approximately 80%.	Ro et al.[77]
72	Syndecan-1	IHC	Down-regulated in 10 to 50% of tumors, depending on the stage.	Kurokawa et al.[48]
39	Syndecan-1	IHC	Decreased expression in 84%.	Mathe et al.[62]
67	P-cad	IHC	Positivity in 55.2%, correlated with a better prognosis.	Lo Muzio et al.[56]
64	E-cad	IHC	Decreased expression.	Santos-García et al.[79]
135	E-cad	IHC	Absent or reduced expression in 60%.	Ueda et al.[103]
47	E-cad	IHC	Reduced expression associated with worse prognosis.	Diniz-Freitas et al.[20]
	E-cad	IHC/RT-PCR	Reduced expression in the invasive tumor front when compared with superficial/center area; related with poor prognosis.	Wang et al. [107]
	E-cad	IHC/RT-PCR	Low expression associated with limph node metastasis.	Foschini et al. [30]
49	E/P/N-cad	IHC	E-cad: underexpressed in 80%; P-cad: overexpressed in 53%; N-cad: negative in 63%.	Pyo et al.[76]
30	E-cad	IHC	Loss of expression in invasive tumor front in 93%.	Mahomed et al.[61]
81	E-cad	IHC	Membrane expression found in 74%/88.9% of early/no recurrence.	Aguiar et al.[14]
135	α/β/y -catenin	IHC	α/β/y-catenin absent or reduced in 72%/58%/59%, respectively.	Ueda et al.[103]
30	β-catenin	IHC	Loss of expression in invasive tumor front in 73%.	Mahomed et al.[61]
81	β-catenin	IHC	Membrane positivity in 70.3%/90.7% of early/no recurrence.	Aguiar et al.[14]
26	CK8	IHC	Positivity in 92%.	Gires et al.[35]
308	CK1,5/6,8/ 1810,14,19	IHC	The expression of CK 8/18 and CK 19 were overall correlated with a poor prognosis.	Fillies et al.[28]
33	CK9	IHC/RT-PCR	Positive rate of 90.9%, with a 2.21-fold increase of mRNA.	Zhong et al.[111]
15	CK17,19,20	RT-PCR	CK17/CK19/CK20 increased in 94.6%/32.1%/12.5%, respectively.	Toyoshima et al.[99]
138	CD44	IHC	Strong intensity was seen in 98% of homogeneously stained tumours.	Kosunen et al.[45]
50	CD44	IHC/WB	CD44 cleavage was positive in 58%.	Takamune et al.[95]
102	CD44	ELISA	Elevated almost 100%.	Franzmann et al.[32]
25	MMP-9	RT-PCR	Overexpression correlated with lymph node metastasis/extracapsular spread.	Zhou et al.[112]
50	MMP-17	IHC/WB	Overexpressed in 46%.	Takamune et al.[95]
53	MMP-9	RT-PCR /IHC	An overall 4-fold increase was observed.	Ye et al.[110]
138	MMP-9	IHC	The intensity was strong in 17%, moderate in 63%, and weak in 20%.	Kosunen et al.[45]
20	Laminin-5	IHC	Positive labeling in 55%.	Lindberg et al.[53]
31	Laminin	IHC	Intense marking 36.8%.	Souza et al.[93]

membrane and are subsequently stimulated to produce MMPs, which begins fragmentation and degradation of the membrane. The ability of malignant neoplasmas to destroy the basal membrane has been correlated with its invasive potential.[105] It has been found to be overexpressed in OSCC within different grades of histological malignancy[105-106] (Table 4).

Conclusions and Perspectives

This article brings a review on the characterization of biological markers in biopsies obtained from OSCCs. Based on these studies, it is possible to observe that several different molecules have been investigated during the last years, and some of them might well represent useful prognostic tools for OSCC. To our knowledge, it is impossible to completely stress all the published studies, but the most relevant markers seem to be represented by EGF and its receptor (which are related to cell proliferation); the tumor suppressor gene p53; the angiogenic molecules VEGF and integrin; as well the regulators of cell adhesion, such as cadherins. In spite of the convincing evidence on the importance of these biological markers, their clinical appliance is still

limited. In this regard, efforts are necessary to establish a better correlation between experimental studies and the clinical scenario. Undoubtably, this would result in a more accurate determination of prognosis and novel therapeutic advances for OSCC.

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