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REVIEW ARTICLE

FUTURE PERSPECTIVES OF EPIGENETIC DRUGS IN ORAL CANCER

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SUMMARY

Oral cancer, predominantly in the form of squamous cell carcinoma, affects 500,000 people worldwide each year and is the most common head and neck cancer. Major risk factors are the use of tobacco and alcohol consumption, which induce multistep carcinogenesis and multifocal neoplastic lesions in the exposed epithelial field. There have been major improvements in the treatment of oral cancer thanks to surgical techniques, radiotherapy, chemotherapy and gene therapy. In addition to genetic changes, epigenetic modifications play a pivotal role in the development of this neoplastic disease. Epigenetics is defined as the study of mitotically and/or meiotically heritable changes in gene function that cannot be explained by changes in DNA sequence. Epigenetics has allowed a novel molecular vision of organisms, and provides alternative solutions to the reductionist genetic approach, providing explanations to the regulatory mechanisms of gene expression by DNA and chromatin modifications. DNA methylation triggers histone deacetylation, chromatin condensation, and gene silencing. We will discuss briefly these epigenetic "marks" and their important implications in cancer screening. Used in early detection, prevention, classification for epidemiology and prognostic purposes, novel epigenetic drugs show favorable clinical outcomes and promising preliminary data.

INTRODUCTION

Oral cancer, or oral cavity cancer, is part of a group of cancers classified as head and neck cancers and includes cancerous tissue growth originated in any of the tissues of the oral cavity or oropharynx of varied histologic types: 1) squamocellular carcinoma from the epithelium of the oral mucosa; 2) adenocarcinoma derived from a major or minor salivary gland; 3) lymphoma from tonsillar or other lymphoid tissue; 4) teratoma; or 5) melanoma from the pigment-producing cells of the oral mucosa. It most commonly involves the tissue of the lips (particularly lesions of the lower lip) or the tongue (lateral border, especially posterior). Other common sites are the floor of the mouth, the cheek lining, the gingiva or the palate. More than 90% of all diagnosed malignant oral cancers are oral squamous cell carcinoma (OSCC) (1).

Oral cancer is in the top 10 of the most common neoplasms in the world. There is an exceptionally high occurrence in Northern France, Eastern Europe (particularly Hungary), parts of South America and Southeast Asia (1). Among the 34,000 persons diagnosed in the U.S. every year, 66% are already in late stage III or stage IV, resulting in over 8,000 deaths every year, or 1 death every hour. The roughly 50% 5-year survival rate has not significantly improved in decades, and its prognosis is poorer than that of more widely recognized diseases, such as cancer of the testes, thyroid cancer or malignant melanoma.

As of today, Medline contains approximately 78,000 papers linked to the keyword "oral cancer", reflecting the worldwide scientific interest for a disease that accounts for 500,000 new cases each year (2).

Although heredity may be a risk factor, oral cancer predominantly occurs due to preventable lifestyle choices and health conditions (3). These include, but are not limited to, tobacco and alcohol use, sunlight, chronic irritation due to poorly fitted dentures, periodontal disease, lack of fruits and vegetables in the diet, consumption of spicy food, alcohol-containing mouthwash, human papillomavirus (HPV) infection and immune system suppression (4). Smoking and other tobacco use, in particular, are associated with about 75% of oral cancer cases. Although smokeless tobacco contains more nicotine than cigarettes and the cancer risk of smokeless tobacco users is probably lower than that of smokers, it is higher than that of non-tobacco users. Additionally, in many Asian cultures chewing betel, paan and Areca is known to be a strong risk factor for developing oral cancer (5). In young nonsmokers, type 16 HPV transmitted between part-

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ners is also suspected as a factor (6). The 2:1 ratio of incidence between men (particularly those between the ages of 40 and 60) and women is gradually decreasing due to lifestyle changes, especially in African American female smokers (7). Lip cancer is also related to exposure to ultraviolet irradiation, especially in fishermen, farmers, skiers and windsurfers; however, due to early detection there is a 95% 5-year survival rate (1).

The treatment of oral cancer usually requires a multidisciplinary approach consisting of diagnosis, treatment, rehabilitation and patient care. It often involves experts in radiation, surgery, chemotherapy, genetics and epigenetics, nutrition, dentistry and psychology. Surgical therapeutic modalities, such as maxillectomy, mandibulectomy, glossectomy, radical or functional neck dissection, or combinational surgery (e.g., involving multiple organs), are effective treatments if the tumor is relatively small and has not metastasized. However, these treatments are frequently limited by the complexity of the anatomy, as well as cosmetic and functional considerations. Radiation therapy is often used in conjunction with surgery, or as the definitive treatment, especially if the tumor is inoperable. Approximately 80-100% of the patients receiving radiotherapy develop oral mucositis, necessitating therapy discontinuations and/or reductions in radiotherapy doses. These patients can be treated with the antioxidant vitamin E, which decreases the severity of oral mucositis, but also promotes tumor recurrence (8). Chemotherapy (intra-arterial, intralesional) is seldom used alone, but is useful in combination with other treatment strategies such as radiation therapy. Also, vaccines against HPV are being studied, since it is involved in a subset of oral cancers (8).

Interstitial photodynamic therapy uses optic fibers to activate cytotoxic agents specifically at the tumor site. A phase I/II study in 45 patients sensitized with Foscan® (temoporfin, mTHPC; Biolitec Pharmaceuticals, Ltd.) resulted in minimal morbidity and preserved oral appearance (9). Ancient remedies, including green tea and combrestatin from the bark of an African tree, have also been proposed in combination with modern therapies, but these nonconventional treatment modalities have been debated (10, 11).

Monoclonal antibodies such as cetuximab (IMC-C225, Erbitux®; marketed in North America by ImClone and Bristol-Myers Squibb, and outside the U.S. by Merck KGaA) have been successful in reducing or eliminating oral cancers by blocking epidermal growth factor receptor (EGFR), when given along with radiation. Cetuximab used alone as monotherapy can cause rash, fever, chills and nausea. Erlotinib (Tarceva®; marketed in the U.S. by Genentech and OSI Pharmaceuticals, and elsewhere by Roche), a tyrosine kinase inhibitor, also blocks EGFR, and when given orally appears to benefit some patients. Cetuximab and another EGFR-selective tyrosine kinase inhibitor, AG-1478, dose-dependently inhibited OSCC when administered with cisplatin. The above EGFR inhibitors may represent a novel strategy for overcoming resistance to cisplatin-mediated apoptosis via the phosphatidylinositol 3-kinase/Akt pathway (12).

Oncogenesis specifically relevant to oral and oropharyngeal cancers has also been studied. For example, the oncogene *KLF4* (or *GKLF*) may play a key role (13). New discoveries in gene therapy are being applied to experimental treatments in an attempt to reverse genetic alterations in these cancers. Clinical trials are currently testing whether it is possible to replace abnormal tumor suppressor genes (i.e., the *TP53* gene) of oral cancer cells with a normal copy to restore normal cell cycle and growth control (14). In a recent study, functional genomics of primary keratinocytes from different transgenic mouse cell lines and immunostaining of mouse and human samples were performed in order to identify candidate biomarkers of oral cancer progression. Additionally, tissue microarray analysis of human samples confirmed the association between active Akt and increased *KLF4* expression. The authors suggested that *KLF4* is potentially a reliable marker of head and neck squamous cell carcinoma (HNSCC), and that myrAkt transgenic mice (expressing high levels of constitutive Akt activity) are valuable tools for preclinical research (13).

Besides genetic changes, epigenetic aberrations in conjunction with dysregulated signal transduction pathways of cell proliferation and survival are crucial to the development of oral cancer. In this review, we will provide a mechanistic insight of demethylating agents and histone deacetylase (HDAC) inhibitors under development. This new class of drugs is expected to offer an additional point-of-attack approach towards improving long-term prognosis and quality of life for oral cancer patients.

EPIGENETICS EXPLAIN WHAT GENETICS CANNOT

Genetic analysis provides diagnosis and therapy for various diseases and aging. However, gene changes alone cannot explain the entire cancer scenario (15). Most of the epigenetic alterations are reversible in vitro and in vivo, leading the way to the development of new anticancer therapies (16).

Regulation of gene expression can be obtained through epigenetic changes that affect the methylation or the acetylation status of genomic DNA in eukaryotic cells. DNA methylation is the addition of a methyl group to a cytosine (C) in the genomic DNA of a cell. This occurs only when C is followed by a guanine (G) in so-called "CpG pairs", and when clustered together form the "CpG islands". Methylation of promoter-associated CpG islands can be physiological, as in the imprinted genes or X-linked genes in females, or pathological, resulting in aberrant gene silencing by deletion or by inactivating mutations. DNA methylation is mediated by enzymes with DNA methyltransferase (DNMT) activity. DNMTs are inhibited by drugs such as 5-azacitidine and decitabine.

The HDAC family consists of 18 members divided phylogenetically into 5 classes, all of which are Zn^{2+}-dependent, with the exception of class III, which are NAD^{+}-dependent (Table I). Acetylation of histones in specific lysine residues is a bona fide positive activating histone "mark". Levels of histone acetylation are determined by interplays of acetylation and deacetylation catalyzed by histone acetyltrasferases (HATs) and HDACs, respectively (Fig. 1). The HATs are grouped into six evolutionarily conserved major families: MYST, GNAT, KAT2B, TFIIIC, p160 and "orphans" (17). Silencing of tumor suppressor genes is often associated with local deacetylation of histones and with genomic regions containing DNA methylation, as well as methylation at lysine residues 9 and 27 of histone H3, and lysine residue 20 of histone H4. On the other hand, activation of gene expression, including activation of oncogenes, is associated with locally acetylated histones and methylation at lysine residues 4, 36 and 79 of histone H3.

Table I. *Histone deacetylases (HDACs) are enzymes that remove acetyl groups from an ε-N-acetyl lysine amino acid on a histone. The HDAC family classification is shown here in order of their sequential identity and domain organization.*

Class	Histone	Substrate	Homology to	Localization
Class I	HD1	Histone H2A, 2B, 3, 4, AR, ER, SHP, YY1		
	HD2	H2A, 2B, 3, 4, GR, YY1		
	HD3	H2A, 2B, 3, 4, GR, SHP, GATA-1, YY1	Yeast *RPD3* gene	Nucleus
	HD3	H2A, 2B, 3, 4		
Class IIa	HD4	H2A, 2B, 3, 4, GATA-1		
	HD5	H2A, 2B, 3, 4, GATA-1		
	HD7A	H2A, 2B, 3, 4	*HdaI* gene	Nucleus/cytoplasm
	HD9	H2A, 2B, 3, 4		
Class IIb	HD6	H2A, 2B, 3, tubulin, SHP	*HdaI* gene	Nucleus/cytoplasm
	HD10	H2A, 2B, 3, 4		Mostly cytoplasm
Class III	SIRT1, 6, 7			Nucleus
	SIRT2			Cytoplasm
	SIRT3		*SIR2* gene	Nucleus/mitochondria
	SIRT4	Non-histone proteins		Mitochondria
	SIRT5	Tubulin, p65, p53		
Class IV	HD11	H2A, 2B, 3, 4	Yeast *RPD3* gene	Nucleus/cytoplasm

AR, androgen receptor; ER, estrogen receptor; GR, glucocorticoid receptor.

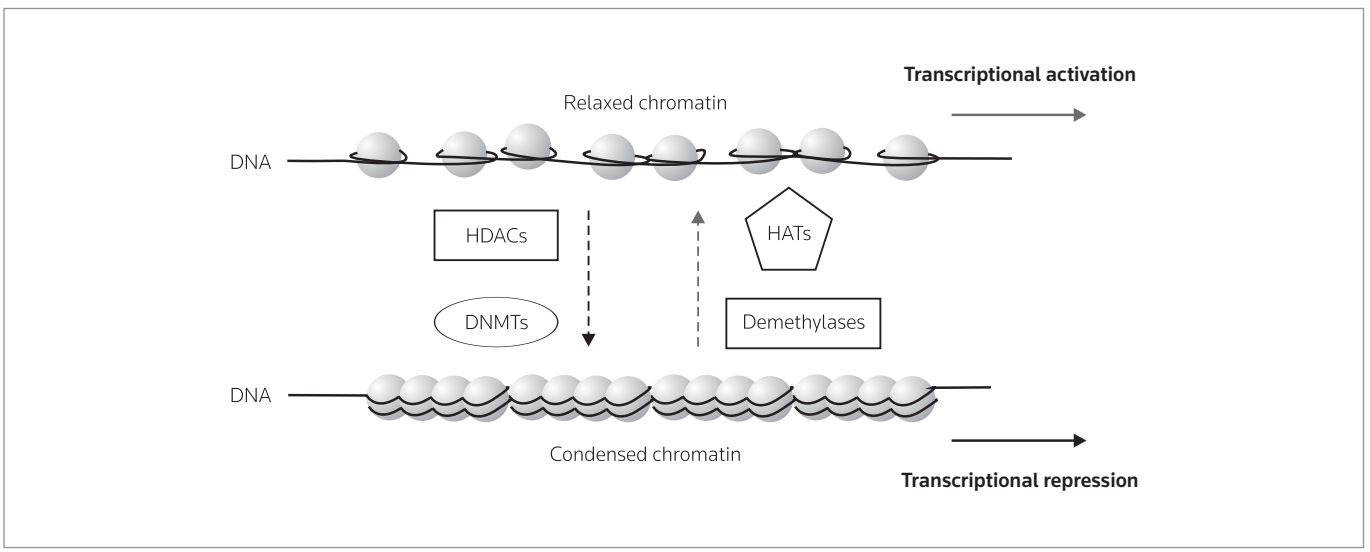

Figure 1. Chromatin remodeling showing the fundamental histone "marks" (both closed and silenced, and the relaxed and activated status), and the effects of epigenetic drugs. HDACs, histone deacetylases; HATs, histone acetyltransferases; DNMTs, DNA methyltransferases.

EPIGENETIC DRUGS AND CLINICAL RELEVANCE

Scientific breakthroughs for epigenetic treatment of oral cancer

Epigenetic alterations, represented by aberrant DNA methylation of tumor suppressor genes, are deeply involved in human cancers. Altered DNA methylation, in the form of regional hypermethylation and global hypomethylation, is one of the most consistent changes in cancer. The reaction mechanism of DNMT, which includes the formation of a covalent intermediate between the enzyme and the target base, is the basis of the success of several anticancer drugs. The DNMT inhibitors used are 5-fluoro-2′-deoxycytidine, decitabine and zebularine. In particular, in 2004, azacitidine (Vidaza®; Pharmion) for injectable suspension received regulatory approval by the FDA for the treatment of all subtypes of myelodysplastic syndrome. Decitabine is even more potent, albeit with side effects, including bone marrow suppression. Therefore, there is a need for less toxic DNMT inhibitors. Recently, zebularine, a derivative of 5-azacytidine, was developed as a less toxic analogue in an oral formulation. However, its oral bioavailability is not as favorable in monkeys as in mice (18).

Histone deacetylase inhibitors (HDIs) have attracted a great deal of interest as drug targets in recent years (Table II). Most of the HDIs currently in the clinic are "broad-spectrum" or "pan-HDAC" inhibitors, such as vorinostat (Zolinza®), panobinostat, PCI-24781, belinostat, JNJ-26481585 and givinostat hydrochloride. In particular, vorinostat showed very favorable activity in a phase II clinical trial in patients with cutaneous T-cell lymphoma. Other class I HDACs inhibitors are "isotype-specific", including compounds such as romidepsin, entinostat, mocetinostat and the short-chain fatty acids valproate and butyrate (19).

The HAT inhibitors are classified into two groups. The first group includes the natural compounds curcumin (the most studied), anacardic acid and garcinol, all obtained from plant extracts and potent inhibitors of p300. The second group consists of the synthetic compounds bisubstrate, garcinol analogues, γ-butyrolactone, MB-3, quinoline and isothiazolone derivatives. These synthetic compounds have so far demonstrated high efficacy in the prevention and therapy of colorectal, prostate, kidney, lung, ovarian, breast, cervical and liver cancers (17).

Demethylating agents

Huang et al. investigated the methylation status of genes by polymerase chain reaction–denaturing high performance liquid chromatography (PCR-DHPLC) (avoiding methylation-specific PCR to prevent overestimation) in the Ras/PI3K/Akt pathway in 482 Taiwanese patients with oral squamous cell carcinomas (196 treated with surgery only and 286 treated with radiotherapy after surgery). The authors found that *RASSF1A, RASSF2A* and *HIN1* genes are hypermethylated and indicative of poor prognosis in patients treated with radiotherapy after surgery, but not in patients treated with surgery alone. Their results point to the role of epigenetic silencing of the above pathway in the development or progression of squamous cell carcinoma, and exemplify the need to exploit demethylating agents to overcome radioresistance (20).

Zebularine is a structural analogue of cytidine, and it is interesting in that it inhibits cytidine deaminase and DNA cytosine methyltransferase. Zebularine has a favorable pharmacokinetic profile and is very cancer cell-selective. It has proven effective in animal models and can be administered orally (21, 22). Zebularine is effective in combination with 5-fluorouracil (involving the cAMP/PKA/CREB pathway in HSC-3 OSCC cells), but not with cisplatin (23, 24).

Baba et al. generated a mouse model of carcinogenesis using 4-nitroquinoline 1-oxide (4NQO) coupled with oxidative stress in target cells. They went on to use DNA methyltransferase 1 (Dnmt1) hypomorphic alleles to prevent in part genomic methylation. Histology demonstrated that the resulting global hypomethylation had a suppressive effect on squamous carcinogenesis in the tongue and esophagus. As a conclusion, the authors suggested that the pharmacological modification of the epigenetic status may be useful for the prevention and treatment of the above cancers (25).

A recent study analyzing 40 oral cancer cell lines and 50 primary oral tumors, revealed frequent silencing of the putative tumor suppressor gene *MTNR1A*. *MTNR1A* encodes one of two affinity forms of a melatonin receptor involved in the modulation of circadian rhythms. Silencing was avoided by treatment with decitabine (26). An earlier study on cancer cell lines and clinical tumors probing the role of the tumor suppressor gene *PTEN* on the basis of methylation in nine OSCC-derived cell lines did not show promising activity for the demethylating agent decitabine (27).

A recent report has linked the tuberous sclerosis (TSC) tumor suppressor genes and other members of the mTOR signaling pathway with methylation status in the pathogenesis of OSCC. Semi-quantitative realtime (RT)-PCR analysis showed downregulation of *TSC1, TSC2*, *EIF4EBP1* and *PTEN*, and upregulation of *PIK3C2A, AKT1, PDPK1, RHEB, FRAP1, RPS6KB1, EIF4E* and *RPS*6 in tumors. Investigation of the mechanism of downregulation of TSC genes identified loss of heterozygosity (LOH) in 36.96% and 39.13% of the tumors, respectively, at the *TSC1* and *TSC2* loci. In just one OSCC cell line, treatment with azacytidine showed an increase in the expression of the *TSC1* and *TSC2* genes, suggesting promoter hypermethyl-ation as a mechanism for their downregulation. However, the treatment of non-OSCC HeLa cells with azacytidine showed a significant increase in the expression of only the *TSC2* gene. The methylation status of the *TSC2* gene promoter was confirmed in patient tumor samples by combined bisulfite restriction analysis (COBRA). LOH and promoter methylation are proposed as the two important mechanisms for downregulation of TSC genes. So far, no correlation can be established with clinicopathological parameters, such as age, sex, T classification, stage, grade, histol-

Table II. *The histone deacetylase (HDAC) inhibitor (HDI) classification below is based on a reproduction. The "classical" or "first-generation" inhibitors block class I and II HDACs by binding to their catalytic domain containing Zn^{2+}. The classical HDI subgroups shown are in order of decreasing efficiency.*

HDAC inhibitors	A) "Classical" or "first-generation"	1) Hydroxamic acids (i.e., trichostatin A) 2) Cyclic tetrapeptides (i.e., trapoxin) and depsipeptides 3) Benzamides 4) Electrophilic ketones 5) Aliphatic compounds (i.e., phenylbutyrate, valproic acid)
	B) "Second-generation"	a) Vorinostat b) Belinostat c) Dacinostat d) Panobinostat e) Eutinostat f) Tacedinaline g) Mocetinostat

ogy, tobacco habits, lymph node metastasis and presence or absence of LOH at the *TSC1* and *TSC2* loci (28).

Suzuki and collaborators used comparative genomic hybridization (CGH) arrays to identify a homozygously deleted region comprising a possible tumor suppressor gene, *PRTFDC1*. The authors identified a functional CpG island around exon 1 of the *PRTFDC1* gene. Hypermethylation of this gene leading to a loss of function was correlated with OSCC in cell lines and primary tissues, pointing to a pathogenetic role and to its possible usefulness as a diagnostic and prognostic marker (29).

Among genes establishing the epithelial cell phenotype, *CDH1* is the one most often implicated as having a regulatory role in tumorigenesis and progression. A study determined the methylation status within CpG islands of the *CDH1* promoter region in relation to the expression of SMADIP1, a major *CDH1* repressor in oral carcinoma cells. Methylation-PCR and PCR-fragment length polymorphism analyses showed that *CDH1* was downregulated, the mechanism being promoter hypermethylation. Interestingly, treatment with decitabine induced upregulation of *CDH1*, but only in a fraction of the cancer cell lines. However, nonresponsive cell lines consistently had high expression of SMADIP1, whether or not the promoter was methylated (30). The methylation status of the *APC* gene, a known tumor suppressor gene originally identified in colon cancer, has also been investigated in tissue samples and OSCC cell lines. In about two-thirds of the cases in which *APC* was downregulated, hypermethylation of the gene promoter was detected and decitabine consistently restored *APC* expression (31).

HDAC inhibitors

In an effort to achieve organ preservation and local control in oral carcinoma, radiation has been a mainstay of therapy in the definitive, adjuvant or salvage setting. However, the majority of the patients receiving radiation therapy develop oral mucositis. Chung et al. used a male Syrian golden hamster model to show that the HDAC inhibitor phenylbutyrate inhibits chemical-induced tumors. Phenylbutyrate is also radioprotectant, promoting normal cell DNA repair and survival after radiation-induced DNA damage (32).

Valproic acid may be an effective drug for the development of better therapeutic regimens for HNSCC. Indeed, valproic acid acts as an HDAC inhibitor in squamous cell carcinoma (SCC) cells and normal human keratinocytes (HKs), reinforces the cytotoxic effect of cisplatin in SCC cell lines and decreases the viability of SCC cells as opposed to HKs (33). Other HDAC inhibitors have a potential anticancer effect, although their efficacy has not yet been confirmed in oral cancer (34). For example, romidepsin, a natural prodrug that inhibits class I HDACs, suppressed the proliferation of human prostate cancer cells in vivo with no adverse effects (35).

Mocetinostat dihydrobromide, an isotype-selective inhibitor of mostly class I HDACs, was administered orally 3 times weekly without interruption in a phase I study in 29 patients with leukemia or myelodysplastic syndromes. In this study, mocetinostat was safe and it had antileukemia activity in an early preclinical study (36).

Phenylbutyrate, an aromatic fatty acid with multiple mechanisms of action, including HDAC inhibition, was tested in a phase I trial conducted in 28 patients with refractory solid tumor malignancies to evaluate toxicity, pharmacokinetic parameters and feasibility of p.o. administration.

CONCLUSIONS AND FUTURE DEVELOPMENTS

Novel epigenetic agents

The current pharmaceutical efforts in the development of newer hypomethylating agents is practically negligible compared to the large number of new HDAC inhibitors. While new formulations of current drugs already in use, such as the oral formulation of azacitidine (36), are still very welcome, it is difficult to predict if preclinical studies specifically focused on OSCC will be initiated. Other potential future targets for oral anticancer therapeutic interventions include histone methylation and phosphorylation. Aurora kinases A, B and C are members of the serine/threonine-protein kinase family and play an important role in mitosis. They are essential for spindle assembly, centrosome maturation, chromosome segregation and cytokinesis during mitosis (37). Abnormalities in the mitotic process as a result of overexpression/amplification of Aurora kinase have been linked to genomic instability, leading to tumorigenesis. Approximately 150 patents and 700 scientific journal articles are available on small-molecule Aurora kinase inhibitors (37). OM137, a novel Aurora kinase inhibitor, exhibited growth-inhibitory effects alone and reinforced the inhibitory effects of paclitaxel, a known chemotherapeutic spindle poison (38). The pentacyclic inhibitor AKI-001 showed high potency in a mouse xenograft model and oral bioavailability (39). The small-molecule inhibitor tozasertib led to apoptotic cell death in OSCC cells, suggesting a promising future for Aurora kinase inhibitors as novel therapeutic agents for this neoplasia (40).

Epilogue

As cancer results from a combination of epigenetic and genetic aberrations, epigenetic and genetic therapies are viewed as a key addition to cytotoxic agents in order to leap forward in the prognosis of cancer. There is also the possibility of using these agents as maintenance therapies or sensitizing agents prior to standard chemotherapy, or even as prophylactic treatments in patients at high risk of developing malignancies. However, at some point in the future, as knowledge progresses, epigenetic and genetic therapies are expected to become the mainstay of effective cancer therapy. Aberrant DNA methylation is presently also implicated in disorders with polyclonal origins (41). While neoplastic malignancies are currently the leading clinical indication for these compounds, future applications may include autoimmune diseases, neurological, and even infectious diseases (19).

Demethylating agents may only have a transient effect on treated cells, and abnormal methylation patterns may return with the removal of the drug. For this reason a combinatorial approach is presently preferable, if not mandatory (42). Epigenetic therapy can be used to reactivate tumor suppressor genes and restore the normal function of the cells, and it can also be used in combination with other drugs to increase the efficacy of existing therapies. Epigenetic therapy can be useful for chemopreventive approaches, especially for those individuals who have been diagnosed with aberrant epigenetic alterations, but have not yet acquired neoplastic lesions.

Using easily accessible, small clinical samples we can identify epimutations or aberrant DNA methylation and histone modification patterns in individuals with no history of malignancy as an indicator of the likelihood of developing cancer. Among the present disadvantages of demethylating compounds are their side effects, including emesis and skin rash, and the development of secondary malignancies in animals (but not in humans) at levels not higher than most other anticancer agents; additional follow-up is needed to fully assess this issue (43-45).

The HDAC family is an especially promising class of drug targets due to the importance of these enzymes in cell cycle regulation, metabolism, protein trafficking, DNA repair and angiogenesis. Despite the promise, there is clearly room for improvement of these drugs, which display toxicities including fatigue, nausea, vomiting, thrombocytopenia, neutropenia, and some cardiac toxicity. Toxicity may be reduced by specific inhibition of selected HDAC isoforms, which can only be accomplished in the light of a much more comprehensive knowledge of their biology. Currently, the best specific HDAC inhibitor (targeting HD6, a class IIb HDAC) is tubacin, which does not directly induce apoptosis, but is synergistic with other chemotherapeutics in multiple myeloma (46). Interestingly, HD6 was not affected in human acute myeloid leukemia cells cultured to develop resistance to the pan-HDAC inhibitors (47).

The introduction of hypomethylating agents and HDAC inhibitors in current therapeutic protocols could be a risk-oriented approach with very low doses in lower-risk oral cancer patients and as combination strategies for higher-risk patients. The right drug combinations should produce therapeutic synergy without overlapping side effect profiles. Unfortunately, epigenetic drugs currently lack the necessary specificity to achieve these goals consistently and predictably. Both demethylating and deacetylating agents are used efficiently for the treatment of myelodysplastic syndrome and cutaneous T-cell lymphoma. However, they are not yet part of the therapeutic strategies used against solid tumors such as oral cancer. This may be related to the lower number of proliferating cells. Larger studies will be needed involving analysis of large sets of genes and more adequate animal models. The eventual acquisition of comprehensive knowledge of the epigenome will help not only the treatment, but also the prevention of oral cancer.

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DISCLOSURES

The authors state no conflicts of interest.

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