Advances in the biology of oral cancer

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Summary The incidence of oral cancer remains high and is associated with many deaths in both Western and Asian countries. Several risk factors for the development of oral cancer are now well known, including smoking, drinking and consumption of smokeless tobacco products. Genetic predisposition to oral cancer has been found in certain cases but its components are not yet entirely clear.

In accordance with the multi-step theory of carcinogenesis, the natural history of oral cancer seems to gradually evolve through transitional precursor lesions from normal epithelium to a full-blown metastatic phenotype. A number of genomic lesions accompany this transformation and a wealth of related results has appeared in recent literature and is being summarized here. Furthermore, several key genes have been implicated, especially well-known tumor suppressors like the cyclin-dependent kinase inhibitors, TP53 and RB1 and oncogenes like the cyclin family, EGFR and ras. Viral infections, particularly with oncogenic HPV subtypes and EBV, can have a tumorigenic effect on oral epithelia and their role is discussed, along with potential therapeutic interventions. A brief explanatory theoretical model of oral carcinogenesis is provided and potential avenues for further research are highlighted.

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Introduction
Oral cancer refers to a subgroup of head and neck malignancies that develop at the lips, tongue, salivary glands, gingiva, floor of the mouth, oropharynx, buccal surfaces and other intra-oral locations, according to the International Classification of Diseases (ICD version 9, categories: 140—146, 149). Nevertheless, the term is synonymous to squamous cell carcinoma (SCC) of oral mucosal origin that accounts for more than 90% of all malignant presentations at the aforementioned anatomical sites.¹

More than 300,000 new cases worldwide are being diagnosed with oral squamous cell carcinoma annually.² Approximately 30,000 new cases are recorded annually in the US³ and 40,000 new cases are recorded in the EU.⁴ Oral cancer...
is estimated by WHO to be the eighth most common cancer worldwide. However, the incidence of oral cancer has significant local variation and is increasing in some parts of the world. In India and other Asian countries, oral and oropharyngeal carcinomas comprise up to half of all malignancies, with this particularly high prevalence being attributed to the influence of carcinogens and region-specific epidemiological factors, especially tobacco and betel quid chewing.

Risk factors

The most important risk factor for the development of oral cancer in the Western countries is the consumption of tobacco5 and alcohol.6 Although drinking and smoking are independent risk factors, they have a synergistic effect and greatly increase risk together. In Asian countries, the use of smokeless tobacco products such as gutkha, masala and betel quid7,8 is responsible for a considerable percentage of oral cancer cases.

Several studies have reported a significant familial component in the development of oral cancer. The estimates of risk in first degree relatives of oral cancer patients vary widely and have been reported to be 1.1,9 2.5,10 3.511 or 3.812 in various studies, although it should be noted that some of these studies refer to head and neck cancer in general. Oral cancer patients whose relatives have upper respiratory and digestive tract tumors are also more likely (odds ratio 3.8) to develop a second primary tumor,13 an important cause of treatment failure. Familial aggregation of oral cancer, possibly with an autosomal dominant mode of inheritance, was reported in a very small percentage of oral cancer patients14 but further details are lacking.

The familial risk for oral cancer could be acquired as a result of imitating high risk habits within the family, such as smoking and drinking, or as a genetic trait. Polymorphic variation of genes in the xenobiotic metabolism pathways may be implicated, such as in CYP1A1 or the genes coding for glutathione S-transferase-M1,15,16 and N-acetyltransferase-2.17 Individuals that carry the fast-metabolizing alcohol dehydrogenase type 3 (ADH3) allele18 may be particularly vulnerable to the effects of chronic alcohol consumption and could be at increased risk to develop oral cancer, although newer evidence does not support this association.19,20 A recent review21 has highlighted the necessity for larger and more extensive studies to resolve this issue. Finally, the single nucleotide polymorphism A/G870 in the CCND1 gene that encodes Cyclin D has been associated with oral cancer susceptibility. The AA genotype may increase risk (odds ratio 1.77) for head and neck cancer,22 or oral cancer (odds ratio 2.38).23 Intriguingly, in another study, it was the GG wild-type genotype, instead of the AA genotype, that was associated with increased susceptibility to oral cancer (GG genotype, odds ratio 3.37).24

Staging and prognosis

Staging of oral cancer is conventionally performed with the use of the “tumor, node, metastasis” (TNM) classification system and its variant (pTNM), which are respectively based on clinical and pathological assessment of tumor size and lymph node involvement. However, traditional staging is often inadequate and does not always provide accurate prognostic information. New tumor characteristics, such as loco-regional control,25 extent of recurrence,26 maximum tumor thickness,27 differentiation grade and mode of invasion,28 are being utilized to refine prognosis and allow the selection of appropriate treatment.

Therapy

The therapy of oral cancer is not always satisfactory. Early stage (I and II) oral cancer may be curable by surgery or radiation therapy alone but advanced cancers (stage III and IV) are generally treated by surgery followed by radiation therapy.29 Using multimodal protocols that combine surgery with pre-operative or post-operative radiotherapy and/or adjuvant chemotherapy the 2-year and 5-year survival rates for advanced cancers were as low as 20% and 12%, respectively.30 In fact, survival of advanced-stage patients rarely exceeds 30 months, even for those that initially achieve complete clinical remission.31 Furthermore, most oral SCCs exhibit limited responsiveness to common cytotoxic drugs, due to mechanisms that either block the transport of these agents into the cells or interfere with their intracellular molecular targets.32 Fortunately new sensitive kits for early tumor detection are being developed33 many of which are based on the molecular analysis of exfoliative cytology34 or saliva.35,36 Clearly, a better understanding of the molecular profile of oral cancer should facilitate the development of more efficient targeted therapies.

The genetic evolution of oral cancer

The multi-step model of carcinogenesis is widely accepted37 and requires the step-wise transition from pre-malignant lesions to the metastatic tumor phenotype. A variety of alterations accumulate to potentiate this transition38 and gradually increase malignancy. A similar progression has been shown to occur in oral cancer39 from benign hyperplasia, to dysplasia, to carcinoma in situ and advanced cancer with accompanying genomic alterations.

Several oral lesions are of particular relevance to oral cancer: oral leukoplakia,40 oral lichen planus41 and oral erythroplakia.42 Oral leukoplakia is a clinical diagnosis that describes white patches or plaques that cannot be attributed to any other disease. It is common, especially in older men, and is associated with a variable risk of underlying epithelial alterations depending on its location. Approximately 10–15% of oral leukoplaikias will be diagnosed as mild or moderate dysplasia and another 5% may be diagnosed as severe dysplasia or carcinoma in situ.43 The long term risk of progression to invasive cancer varies between studies from 4% to 18%44–46 and warrants careful clinical management. Oral lichen planus is also quite common and is estimated to incur a 1–4% risk of subsequent cancer development.47,48 Oral lichen planus is believed to be an autoimmune disease and the mechanism of its malignant conversion is not yet well understood. Oral erythroplakia is rare but has a very high risk of progression (14–50%) and is frequently diagnosed histologically as carcinoma in situ or severe epithelial dysplasia.
Oral leukoplakia, oral lichen planus and oral erythroplakia can show varying degrees of histological abnormalities, from mild dysplasia to carcinoma in situ. A subset of these lesions will progress to oral cancer and warrant early and aggressive treatment while others may progress slowly, if at all. This progression has been linked to the presence of genomic instability and the appearance of extensive genomic alterations, such as aneuploidy. Indeed, the evaluation of influential genomic alterations may supplant traditional markers that are unable to predict the time course of pre-malignant lesions.

**Genomic alterations**

**Theory of field cancerization**

The aggregation of genomic alterations during phenotypic progression is assumed to happen in a wide population of cells, a heterogeneous "field of genetically altered cells" that is expected to give rise to precursor lesions. This theory, first proposed by Slaughter et al., attempts to explain the frequent local recurrence and the emergence of second primary tumors in oral cancer. According to a recent adaptation of this concept, the genetically altered cells will gradually proliferate and expand into a non-invasive field that is vulnerable to further genomic damage. This field, despite being macroscopically undetectable, is fertile ground for the evolution of pre-malignant lesions and eventually invasive cancer. Although local excision can completely remove an oral carcinoma, the field may persist and the patient can be at risk for the subsequent appearance of a second tumor from the same field. The exact molecular characteristics of a susceptible genetically altered field are not clearly defined, but key tumor suppressors such as TP53, CDKN2A, and the pRb pathway are likely to be compromised from its early stages.

**Common chromosomal aberrations**

A large variety of chromosomal aberrations can be found in most cancer types, including oral cancer. A summary of aberrations reported in many published studies in oral cancer or head and neck cancer appears in Table 1. The impact of these aberrations varies significantly and their cellular and clinical significance is frequently uncertain. It is generally believed, though, that the number of aberrations increases steadily during cancer progression: oral leukoplakia has fewer chromosomal aberrations than oral cancer, and lower tumor stage (T1) is associated with fewer aberrations than higher tumor stage (T2).

Some aberrations have been described as early, or common, and may bear considerable prognostic significance for patients with pre-malignant lesions or early stage oral cancer. Such aberrations may be linked to important target genes like TP53 in 17p13, RB1 in 13q14 or the CDKN2A gene in 9p21. In particular, several reports indicate the high prevalence of LOH or homozygous deletions in 3p, 9p, 13q and 17p in early oral lesions. Chromosome 9 is believed to be one of the earliest targets and allelic losses in the 9p21 region, possibly associated with the genes encoding the p16 and p14 cyclin-dependent-kinase inhibitors, are present in pre-malignant lesions and oral cancer. Chromosome 3 frequently hosts allelic imbalance in several regions, especially 3p25, 3p21 and 3p13–14, although the underlying responsible genes are not yet entirely clear. It should be noted that the 3p14 region encompasses the fragile site FRA3B and the FHIT gene and is probably one of the most vulnerable areas of the genome in many cancer types. Aberrations that are usually associated with advanced tumor stage or poor differentiation include allelic losses in 5q21–22, 22q13, 4q, 11q, 18q and 21q. Gains in 3q are also a common finding in advanced oral cancer.

With the advent and popularization of newer, massive methods like comparative genomic hybridization (CGH) and microarray-based CGH a wealth of information regarding the chromosomal aberrations in oral cancer is rapidly becoming available. Nevertheless, due to the variability of the results and their dependence on stage, site and other factors, large studies are required to resolve potential conflicts. Unfortunately, most studies are limited by small sample size and their results cannot be safely generalized. A comprehensive review of chromosomal aberrations in head and neck cancer with a focus on results derived from CGH has been recently published.

**Oncogenes**

Oncogenes are genes that are able to increase malignant potential. Many of the major oncogenes that are implicated in other cancer types also contribute to oral cancer. A large
number of these genes promote unscheduled, aberrant proliferation, override the G–S, G–M and M checkpoints of the cell cycle, prevent apoptosis and enable cellular survival under unfavorable conditions.

Growth receptors are known to induce different cellular responses in response to the binding of specific ligands that represent external stimuli. The ErbB family of receptors and the epidermal growth factor receptor in particular (EGFR, also known as ErbB1 or Her-1) has received attention due to its inherent ability to stimulate the proliferation of epithelial cells. Amplification of EGFR is found in a considerable percentage of oral tumors and also in pre-malignant lesions. Although several studies demonstrate the association between EGFR overexpression and tumor grade or stage there are few studies that determine its practical clinical usefulness. EGFR overexpression was reported to be an independent prognostic marker of survival in betel quid chewers and a component of a prognostically significant molecular profile. The usefulness of gefitinib ("Iressa"), a recently developed EGFR inhibitor, has been evaluated in oral cancer cell lines, oral cancer xenografts in mice and patients with advanced head and neck cancer with mixed results, but large-scale human studies of its efficiency in oral or head and neck cancer are lacking.

Other members of the ErbB family are also able to exert transforming effects. ErbB2 (also known as Her-2 or Neu) amplification has been found in oral cancer specimens, non-dysplastic oral leukoplasia and patient sera. Notably, ErbB2 over-expression seems to be more frequent in oral cancer than in head and neck cancer. High levels of ErbB2 may be associated with worse prognosis. A novel monoclonal antibody against Her-2 (trastuzumab) may serve as targeted adjuvant therapy for a sub-group of patients in the future, but extensive trials are required to justify its use in oral cancer.

Signal transduction from activated transmembrane receptors like EGFR depends on a variety of downstream mediators that are frequently altered in various cancer types. A nodal example is the ras gene family that includes the H-, K- and N-ras oncogenes. Indeed, constitutive activation of the K-ras protein in a mouse model is sufficient to induce oral tumor formation. Nevertheless, the frequency of ras gene mutations is estimated to be approximately 0–10% in the USA, Europe and Japan. Very different results have been reported in India, where H-ras and K-ras mutations may be present in 28–35% of tumors. Interestingly, a recent study has shown significant risk (odds ratio 1.6) associated with an H-ras gene polymorphism in the Indian population. Downstream components of the signal transduction cascade, like Raf and ERK and other MAP kinases, have received relatively less attention and are less well studied.

The cyclin family of proteins is tightly coupled with cell cycle progression and its various members are expressed in sequence to enable cycle phase transitions. The D-type cyclins are able to initiate the G–S transition by phosphorylating the retinoblastoma protein in response to mitogenic signals. Abundant expression of cyclin D is a common feature of oral cancer and pre-malignant lesions. Cyclin D overexpression or, more specifically, CCND1 gene amplification may predict worse prognosis and a greater risk of occult cervical lymph node metastasis in low stage tumors. Furthermore, as discussed above, a cyclin D single nucleotide polymorphism has been associated with susceptibility to oral cancer. Cyclin A overexpression, which is closely associated with the presence of S-phase cells, has also been observed immunohistochemically and was most prevalent in advanced tumors. Similarly, Cyclin B, was overexpressed in 37% of tongue tumors and in oral cancer in general.

Angiogenesis, the formation of new vessels from pre-existing ones, is a crucial step in tumor growth, progression and metastasis. Regulation of angiogenesis in vivo is complex and is controlled by a variety of factors. Among them VEGF (vascular endothelial growth factor) is considered to play a dominant role. It has been well established that VEGF promotes the progression of OSCC by up-regulating MVD (microvessel density). Its enhanced expression in oral malignant tumors may be triggered by a hypoxic stimulus. Furthermore, VEGF-C expression has been reported to be a reliable predictor of regional lymph node metastasis in early OSCC. The expression of Flt-4, a member of the family of VEGF receptors, has also been reported to correlate with lymph node metastasis, which agrees with its preferential expression in lymphatic endothelium.

Matrix metalloproteinases are zinc metalloenzymes with the ability to degrade the components of the ECM (extracellular matrix). Their action is crucial during the progression of cancer since they allow the remodeling of the surrounding healthy tissues and enable local invasion. It has been demonstrated that gelatinases (MMP-2 and -9), stromelysins (MMP-3, -10 and -11), collagenases (MMP-1 and -13) and membrane-bound MMPs (MT1-MMP) are expressed in OSCC and may play a role in its progression. The immunohistochemical expression of gelatinases MMP-2 and -9 is related to the invasive potential of OSCC. However, MMP-2 expression seems to be more prominent than MMP-9 in OSCC samples and correlates with lymph node metastasis. Another interesting finding is the association between the overexpression of MMP-2 and MMP-9 and alcohol consumption, which led the researchers to hypothesize that the contribution of alcohol in the carcinogenetic process of oscc may be attributed to the overexpression of these two enzymes.

Tissue inhibitors of metalloproteinases (TIMPs) bind to the MMPs and inhibit their action. However TIMP-1 and -2 are homologues of erythroid potentiating activity (EPA) factors, which promote the growth of erythroid precursor cells. In this context, TIMP-2 expression correlates with local recurrence and poor prognosis.

Tumor suppressors

Tumor suppressors are genes that prevent cells from acquiring malignant characteristics. Tumor suppressor genes are usually entrusted with the regulation of discrete checkpoints during cell cycle progression and with the monitoring of DNA replication and mitosis. Cellular stress and a variety of insults can activate tumor suppressor pathways to arrest the cell cycle.

The retinoblastoma protein and its associated molecular network are frequent and early targets in many tumor
types. When in a hypo-phosphorylated state, the retinoblastoma protein and the other pocket protein family members p107 and p130 bind and inactivate the E2F transcription factors which are essential for cell cycle progression from G to S. Lack of immunohistochemical pRb expression was found in approximately 70% of oral tumors and 64% of premalignant lesions. Similarly, in a later study, about half of oral cancer specimens did not express pRb and 20% of those that did express pRb only contained the inactive, phosphorylated form. Most importantly, 84% of premalignant lesions and 90% of oral squamous cell carcinomas show altered expression of at least one of the components of the pRb network. The cyclin dependent kinase inhibitors (CDKIs), in particular, are known targets in oral cancer, most likely due to their ability to prevent pRb phosphorylation. The CDKN2A locus that encodes p16INK4A is located in 9p21, one of the most vulnerable areas of the genome in oral cancer, as discussed above. Indeed, lack of immunohistochemical p16 expression can be found in up to 83% of oral tumors and up to 60% of premalignant lesions. The predominant mode of inactivation is allelic imbalance, but point mutations and promoter methylation also occur with lower frequency. The alternative CDKN2A transcript, p14ARF, is also commonly suppressed but down-regulation of other INK4 family members, like p15INK4B, is less frequent. The prognostic significance of p16INK4A levels is uncertain, although a study has reported favorable prognosis for patients overexpressing p16INK4A.

The deregulation of the p53 tumor suppression network is observed in many tumor types, including oral cancer. The p53 protein is able to enforce cell cycle arrest or apoptosis under replication stress, thus halting the proliferation of potentially malignant cells. As mentioned above, loss-of-heterozygosity in the 17p13 region that hosts the TP53 gene is very common in oral cancer. Immunohistochemical evaluation for p53 is positive in up to 57% of oral tumors but is also positive in distant, macroscopically normal areas, in accordance with the theory of "field cancerization". Immunohistochemical p53 overexpression in the normal mucosa is associated with an increased incidence of second primary carcinoma in some studies, but not in others. The prognostic value of the p53 status in oral cancer is uncertain and many studies have not found any impact on patient survival. Nevertheless, p53 expression may predict poor prognosis in the subset of patients with low stage, node-negative disease or in those carrying specific TP53 mutations. Interestingly, tumors with TP53 mutations seem to be more resistant to radiotherapy and this information could be vital for the selection of an appropriate treatment.

Figure 1 offers a simplified model of oral carcinogenesis. The initial alterations seem to occur at the basal cell layer under the influence of smoke, alcohol and/or other carcinogens and may involve deactivation of TP53 and other key tumor suppressors. The transition of normal epithelium to invasive cancer is—more often than not—progressive and is accompanied by "multiple hits" which promote proliferation, angiogenesis, local invasion and, eventually, distant metastatic spread.
Viral infections

Human Papillomavirus (HPV)

A plethora of viral agents have been linked to human tumors. Among these, human papillomavirus (HPV) holds a prominent position. To date, more than one hundred HPV types have been identified, and are referred to as "low" or "high risk" according to their oncogenic potential.161 Two products, in particular, of the early genomic region of high-risk HPVs are capable of forming specific complexes with vital cell-cycle regulators: E6, which binds to p53 and induces its degradation, and E7, which interacts with pRb and blocks its downstream activity. Functional deregulation of these key oncopressors results in uncontrolled DNA replication and apoptotic impairment, and explains the increased tumorigenic ability of high-risk types.162

Research on the participation of HPV in oral carcinogenesis has generated varied results, with the reported infection percentages in potentially malignant and cancerous lesions ranging from 0 to 90%. Controversial reports are mainly attributable to the varying sensitivity of HPV detection techniques that have been applied, such as immunohistochemistry,163 in situ hybridization,164,165 and polymerase chain reaction (PCR) variants,166–168 sometimes followed by Southern169–171 or dot blotting.172,173 Research groups that employed a combination of two or more of the aforementioned assays tended to obtain higher infection rates.174

In a recent study, we investigated the presence of HPV genomic sequences in a series of oral leukoplakias, with histological features of hyperplasia and/or dysplasia, and SCs, with the use of a highly sensitive nested PCR-based approach.175 Viral DNA was detected in 91% of oral lesions, which still represents the highest infection percentage ever reported. The vast majority of specimens harbored high-risk viral sequences, with HPV 16 being the prevailing type. The fact that HPV positivity and genotyping patterns were independent of histology urged us to propose an early involvement of high-risk types in oral carcinogenesis. Several groups have supported the implication of HPV during the early stages of oral neoplasia,169 with some assigning the virus a role in malignant progression176 and others suggesting a "hit and run" action.177 Most study groups have observed no correlation between viral presence and age, gender or cancer differentiation,172,178 although sporadic reports of such associations do exist.174,170

Immortalization of human oral keratinocytes has been achieved through transfection with the early region of HPV 16,179,180 and has provided a useful in vitro system for assessing the involvement of the virus in oral neoplasia. Infected cultured cells accumulate progressive chromosomal aberrations through passages,181 express high levels of de-differentiation markers, such as the nerve growth factor (NGF),182 and reach a growth-independent state, possibly due to autocrine interleukin (IL)-6 production.183 However, despite repeated attempts, HPV 16-immortalized keratinocytes have demonstrated no tumorigenic activity in nude mice,181,184 unless subjected to chronic exposure to the tobacco carcinogen benzo(a)pyrene or other chemicals.184,185 Following carcinogenic treatment, these cells secreted increased levels of VEGF (vascular endothelial growth factor), contained a higher number of integrated viral copies, and exhibited a malignant phenotype in organotypic "raft" culture.185 Furthermore, both benzo(a)pyrene stimulation and HPV 16 infection of cultured oral epithelial cells have been shown to confer anti-apoptotic characteristics, such as downregulation of Fas and Bax, as well as overexpression of Bcl2 via p53 deregulation.186

Taken together, these observations suggest that HPV alone is incapable of inducing malignant transformation. Instead, the tumorigenic action of high-risk HPV probably becomes significant in synergy with chemical carcinogens and other risk factors. Epidemiological data seem to confirm this hypothesis: while the role of HPV in cervical carcinoma is crucial, its contribution to oral cancer is much less spectacular, with an odds ratio reported to range between 1.5 and 4.3.187,188 Furthermore, there seems to be a difference between anatomic locations, with oral cancer being generally less affected by the presence of HPV,188 compared to oropharyngeal cancer and tonsillar cancer in particular. The clinical implications are yet unclear, but HPV positive patients have been reported to be younger, consume less alcohol and tend to have a better prognosis.189

Recent trials have shown that an HPV vaccine can provide effective protection against high risk types 16 and 18190 and the development of associated cervical lesions for up to 4.5 years. There are no data that demonstrate its efficacy in the prevention of oral lesions, but a preliminary study of an HPV DNA vaccine against HPV-associated oral carcinogenesis in mice has produced promising results.191 Clearly, large, prospective randomized trials are needed to document the clinical usefulness of HPV vaccines against oral cancer.

Epstein-Barr virus (EBV)

The Epstein-Barr virus (EBV) is a member of the herpesvirus family. Even though its contribution to the malignant transformation of B lymphocytes has been well established, the influence of EBV in the pathogenesis of oral squamous cell carcinoma remains elusive. It has been reported that EBV is more frequently detected in oral lesions such as oral lichen planus and oral squamous cell carcinoma in comparison with healthy oral epithelium.192,193 In another study, LMP-1, the principal oncoprotein of the virus, has been found in many EBV-positive OSCCs, which means that this latent infection may play a role in the malignant transformation of oral mucosa.194 However, these findings are not universal and several studies195–197 have reported the lack of a conclusive relation between EBV and oral cancer or premalignant lesions. Considerable skepticism is justified, in view of the variability between studies that employ different detection methods and refer to different patient populations.

Hepatitis C virus (HCV)

Oral verrucous and squamous cell carcinomas have been reported in HCV-infected patients198,199 while HCV infection has been found to be more prevalent in patients with oral lichen planus.200,201 However, 1–2% of the patients with oral lichen planus develop squamous cell carcinoma of the
oral cavity, which implies the existence of common patho-
genic mechanisms among them. Finally HCV-RNA strands were detected in OLP tissues and there is evidence to indicate that HCV may occasionally replicate in oral lichen tissue and contribute to mucosal damage.

Conclusion

The study of oral cancer is particularly challenging. Oral cancer is an important cause of morbidity and mortality, especially in developing countries, and its prevalence may rise in the foreseeable future. Advances in diagnosis and treatment have slowly accumulated, but a sound understanding of underlying cell biology is likely to enable further, much-needed progress.

Conflict of interest

We wish to declare that the submitted work is original and has not been submitted or published elsewhere. Also, all authors have read and approved the manuscript and agree with the current submission. Finally, there are no potential conflicts of interest.

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