Seminars in Cancer Biology 92 (2023) 28–41

Contents lists available at ScienceDirect

Seminars in Cancer Biology

journal homepage: www.elsevier.com/locate/semcancer

Role of E2F transcription factor in oral cancer: Recent insight and advancements

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ARTICLE INFO

Keywords:
E2F
Oral cancer
Transcription factors
HPV
Ageing
Therapeutic targets

ABSTRACT

The family of mammalian E2F transcription factors (E2Fs) comprise of 8 members (E2F1-E2F8) classified as activators (E2F1-E2F3) and repressors (E2F4-E2F8) primarily regulating the expression of several genes related to cell proliferation, apoptosis and differentiation, mainly in a cell cycle-dependent manner. E2F activity is frequently controlled via the retinoblastoma protein (pRb), cyclins, p53 and the ubiquitin-proteasome pathway. Additionally, genetic or epigenetic changes result in the deregulation of E2F family genes expression altering S phase entry and apoptosis, an important hallmark for the onset and development of cancer. Although studies reveal E2Fs to be involved in several human malignancies, the mechanisms underlying the role of E2Fs in oral cancer lies nascent and needs further investigations. This review focuses on the role of E2Fs in oral cancer and the etiological factors regulating E2Fs activity, which in turn transcriptionally control the expression of their target genes, thus contributing to cell proliferation, metastasis, and drug/therapy resistance. Further, we will discuss therapeutic strategies for E2Fs, which may prevent oral tumor growth, metastasis, and drug resistance.

Abbreviations: Akt, RAC (Rho family)-alpha serine/threonine-protein kinase; AP-1, Activator protein 1; APAF1, Apoptotic protease activating factor 1; APC/C, Anaphase-promoting complex; AS1, Antisense RNA 1; ASK1, Apoptosis signal-regulating kinase 1; ATM, Ataxia Telangiectasia Mutated; BCL, B-cell CLL/lymphoma; BMP2, Bone morphogenetic protein 2; BRCA, Breast cancer gene; BZLF1, BamHI Z fragment leftward open reading frame 1; CCNA/CCNE, Cyclin; CCND1, Cyclin D1; CCNF, F box protein cyclin F; Cdc, Cell division control protein; CDH1, Cadherin 1; CDK, Cyclin dependent kinase; CENPM, Centromere Protein M ChIP, Chromatin immunoprecipitation; CHK, Checkpoint kinase; CKS, Cyclin Dependent Kinase Regulatory Subunit; c-Myc, cellular Myelocytomatosis; DDR1, Discoidin domain receptor 1; DNA, Deoxyribonucleic acid; DP, Dimerization partner; E2F, Adenoviral early region 2 binding factor; EBNA, Epstein-Barr virus latent antigen; EBV, Epstein-Barr virus; FOXC2, Forkhead box protein C2; HIF, Hypoxia inducible factor; HN1, Hematopoietic and neurologic expressed 1; HNSCC, Head and neck squamous cell carcinoma; HOXB7, Homeobox 7; HPV, Human papillomavirus; HSV, Herpes simplex virus; IL, Interleukin; KIF4A, Kinesin family member 4A; LMP, Latent membrane protein; lncRNAs, long non-coding RNAs; lncPCAT1, Prostate cancer-associated ncRNA transcript-1; LZ, Leuzine zipper; MAP3K5, Mitogen-Activated Protein Kinase Kinase Kinase 5; MB, Marked box; miR/miRNA, Micro ribonucleic acid; MLH, MutL homolog; MSH, MutS homolog; mTOR, Mammalian target of Rapamycin; NF-κB, Nuclear factor-kappa B; NSD2, Nuclear receptor binding SET domain protein 2; OPSCC, Oropharyngeal squamous cell carcinoma; OSCC, Oral squamous cell carcinoma; PI3K, Phosphatidylinositol 3-kinase; PIKK, Phosphoinositide-3 kinase like kinase; PPARγ, Peroxisome proliferator-activated receptor-γ; pRb, Retinoblastoma protein; RAN, Raw areca nut; RPA, Replication protein A; SASP, Senescence associated secretory phenotype; SCC, Squamous cell carcinoma; SCCOC, Squamous cell carcinoma of oral cavity; SCCOP, Squamous cell carcinoma of the oropharynx; SNAIL, Zinc finger protein SNAI1; SNHG12, Small nucleolar RNA host gene 12; SNP, Single nucleotide polymorphism; SOX2, SRY (sex determining region Y)-box 2; SSCRP1, Structure specific recognition protein 1; STAT, Signal transducer and activators of transcription; TCGA, The Cancer Genome Atlas; TEAD4, TEA Domain Transcription Factor 4; TGB, Target gene bias; TGF-β:, Transforming growth factor-β; TP53, Tumor protein 53; TP73, Tumor protein 73; TSCC, Tongue squamous cell carcinoma; UHRF1, Ubiquitin-like with PHD and ring finger domains 1; UTR, Untranslated region; VEGFA, Vascular endothelial growth factor A; Wnt, Wingless; YBX2, Y-box binding protein 2; ZNF750, Zinc-finger protein 750.

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https://doi.org/10.1016/j.semcancer.2023.03.004
Received 13 October 2022; Received in revised form 27 February 2023; Accepted 6 March 2023
Available online 15 March 2023

1. Introduction

Oral cancer comprises 95% of all head and neck cancers that arise in the oral mucosa and encompasses cancers of lip and all sub-sites of the oral cavity and oropharynx [1]. It is the sixth most common cancer worldwide with 90% of the cases being histologically squamous cell carcinoma (SCC) [2,3]. Etiologically, oral cancer is multifactorial and its most common predisposing risk factors include: tobacco, excess alcohol consumption, poor oral hygiene, premalignant conditions, exposure to UV radiations as well as the oral microbiome and exposure to viral infections; as in human papillomavirus (HPV) and Epstein-Barr virus (EBV) [4,5], as shown in Fig. 1. In addition, like most cancers, oral cancer is associated with old age, as cancer cases escalate exponentially over the age of 40, particularly epithelial carcinomas [6]. Nevertheless, although this association has been firmly established [6,7]; therapeutic avenues are yet to respond to this association with clear targeted therapeutic strategies that take into consideration the phenotypic changes associated with the aging milieu.

Oral cancers progress chronologically from hyperplasia to dysplasia and finally carcinoma [8]. At the point of their presentation, they are considered a highly aggressive disease, since in the majority of cases, patients are diagnosed with advanced stages (III-IV) coupled with metastasis to distant organs [9,10]. Prognostic tools include age, presence of lymph node metastasis, primary tumor size and location [11]. Today, the 5-year survival rate of oral cancers is 50% with a significant favorable outcome in women, which necessitates the development of novel therapeutic targets [12]. From a therapeutic standpoint, oral cancers are divided into HPV positive (HPV+) and negative (HPV-) cases, with HPV+ ones being generally more responsive to treatment [13]. Interestingly, when it comes to their molecular pathways, both HPV+ and HPV- cases effect the E2F family of transcription factors albeit via different upstream factors [13]. Therefore, novel targeted approaches are gaining popularity by targeting various specific molecular pathways [14–16], as shown in Fig. 1. In this regard, transcription factors are considered as one of the most favorable therapeutic targets in the management of human cancers, including oral. However, given the crucial role that some of these factors play in normal cellular development, a clear understanding of the effect of different upstream signaling

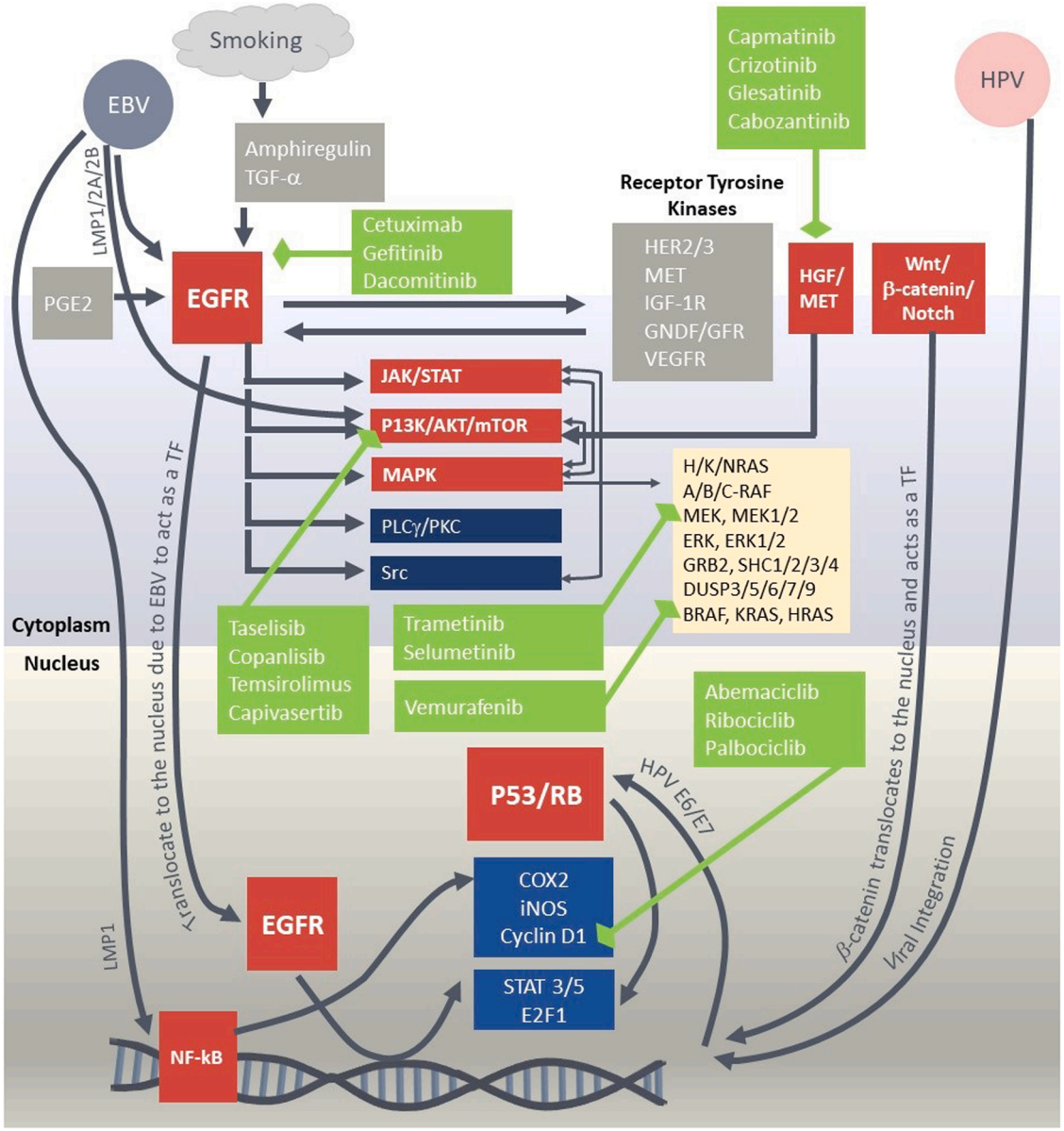

Fig. 1. Major oral cancer signaling pathways (in red), and their downstream targets. Major established therapeutic avenues against oral cancer (in green) and their molecular target.

factors are essential to reach the desired therapeutic outcome.

Transcription factors (TFs) are proteins that identify and bind to DNA regulatory sequences (enhancers and silencers) to induce or suppress gene expression and protein synthesis via the accumulative activity of growth factors, carcinogens, phosphatases and isomerases [17–19]. TFs trigger the onset of several human diseases including neoplastic transformation [20]. Several in-vivo and omic studies (genomic, metabolomic and proteomic) linked alterations of TFs with the onset and development of oral cancers [21–39]; these include, E2F [40], HOXB7 [41], SOX2 [42], AP-1 [21,22,43,44], cMyc [26–28,45], STAT [29–31], NF-κB [23–25,46], Snail [35–37,47] and β-catenin [32–34], which are the most studied TFs affecting the cellular homeostatic balance of the oral epithelium.

When it comes to E2Fs specifically, and given their key role in the cell cycle, they are the most enriched TF in cancer and can be regarded as inducers of various human carcinomas including breast, colon, esophageal, head and neck, kidney, lung, stomach and bladder [48]. Enhanced levels of E2Fs is associated with cancer cell proliferation [49], invasion and metastasis [50] as well as poor prognosis [48] and therapeutic resistance [51]. However, few studies have reported a tumor suppressive role of E2Fs in cancer [52,53]. The discrepancies between these findings remain unclear and need further investigation. This review will provide evidence examining the biological roles of E2Fs in normal and malignant cell development, with a special focus on oral cancer. We will also highlight the current and developing clinical and preclinical strategies to target E2Fs activity in cancer progression and therapeutic resistance.

2. Major signaling pathways of oral cancer

Due to the central role of E2Fs in the cell cycle, they can be inadvertently involved in any type of cell deregulation, which is a hallmark of cancer initiation and progression. Additionally, given the tightly controlled nature of the cell cycle with the various negative/positive feedback loops playing a vital role in its progression, each E2F family member plays a distinct role within these checkpoints. Nevertheless, before detailing E2Fs family of TF, with regards to their structure, function and targets, it is worth reviewing the major pathways of oral carcinogenesis.

These pathways were recently discussed in an article by Li et al. [54]. In summary, major oral carcinogenesis pathways include EGFR, P13K/AKT/mTOR, MAPK, JAK/STAT, HGF/MET, p53/retinoblastoma (RB), Wnt/b-catening and Notch in addition to NF- κB pathways. Additionally, less common oral cancer pathways include VEGF, RET, NRF2, YAP, MST1/2 kinases, SMO and GLI Hedghog pathway proteins as well as TLR2/3/5 [54]. Since these pathways are already detailed in this very recent review, we herein will focus on those that directly target *E2F* transcription, and the etiological factors associated with this activity.

The EGFR pathway is of particular importance since its stimulation via various carcinogens leads to the downstream activation of other well recognized oral cancer pathways, namely: P13K/AKT/mTOR, MAPK and JAK/STAT in addition to Src and PLCγ/PKC [55,56]. Moreover, translocation of this cell membrane receptor to the nucleus under the effect of various carcinogens such as EBV and radiation, allows it to act as a TF that encodes for *COX2*, *iNOS*, and *cyclin D1*. Translocated nuclear EGFR can also lead to signal transduction of *E2F1* and *STAT3/5*, in addition to the phosphorylation of *PCNA*, *DNA-PK* [57–59]. The other major pathway that directly affects *E2F* deregulation is P53/RB, which is highly influenced by HPV infection and its oncogenes, *E6/E7* [60]. Fig. 1 is a schematic representation of the major oral carcinogenesis pathways and their interactions. It is important to note that when it comes to *E2F* function, most signaling pathways involved in cell cycle deregulation, such as aberrant proliferation, growth and metastasis, would affect *E2F* transcription either directly or indirectly via up/downstream signaling, such as P13K/AKT/mTOR, JAK/STAT and MAPK. While others do not seem to have a direct link with *E2F* function, such as those involved in immune evasion. However, in order to elucidate the exact role of E2F TFs in oral carcinogenesis it is important first to examine their role in normal cellular function. Thus, the following sections outline *E2F* family structure, function, target genes and, most importantly, its deregulation in oral carcinogenesis.

3. The E2F family, structure and function

The E2F family of transcription factors consists of eight genes (*E2F1, E2F2, E2F3, E2F4, E2F5, E2F6, E2F7 and E2F8*) encoding 10 proteins that form the central transcription axis in charge of genomic stability by regulating cell cycle progression, cell differentiation, DNA damage repair, metabolism, apoptosis and angiogenesis [61–66]. E2F-encoded proteins consist of either one or more highly conserved DNA binding domains involved in promoter binding [67]. While, alternative splicing and promoter usage of *E2F* genes results in the formation of *E2F* isoforms [68]. To date, alternative splicing of *E2F3* and *E2F7* isoforms have been recognized, four of which, namely, *E2F3a, E2F3b, E2F7a*, and *E2F7b* have been confirmed as part of the TF family [69–71]. While two additional ones have only been recently identified by Araki et al. [72] in cancer cells, *E2F3c* and *E2F3d*, generated from *E2F3a* alternative splicing, that lack DNA binding domains and are localized in the cytoplasm. As such, these two new isoforms may not function as TFs. In this regard, while the role of *E2F3c* is still nascent, *E2F3d* has a mitochondrion targeting signal and seems to play a significant role in hypoxia-induced mitophagy, which is essential for preserving cancer cell mitochondrial integrity [72].

Based on structural features (winged-helix DNA binding domain), the E2F family is classified into two groups, typical E2Fs (*E2F1–6*) and atypical E2Fs (*E2F7–8*) [73,74]. Typical E2Fs consist of a conserved DNA binding domain that binds to the DNA as a heterodimer with dimerization partner (DP) proteins (DP1, DP2 and DP3) mediated by the leuzine zipper (LZ) and marked box (MB) domains [74]. *E2F1-E2F5* consist of a C-terminal transactivation domain and a pocket protein binding region allowing their regulation via the pocket or "retinoblastoma family" proteins (pRb, p107 and p130) [75]. However, *E2F6* consists of a C-terminal with a binding region that allows it to couple with the Poly-comb group [76]. *E2F1–3* have a nuclear localization signal and a cyclin A binding site in the N-terminus, thus enhancing their nuclear translocation to regulate cell cycle activity [77,78]. While *E2F4–5* have bipartite nuclear export signals to promote their cytoplasmic translocation [79,80]. On the other hand, atypical E2Fs consist of two unique DNA binding domains allowing them to bind to DNA as homodimers or heterodimers [74] with the absence of pocket protein binding regions and transcriptional activation domains [81,82]. Fig. 2 details the structural features of *E2F* family members.

E2Fs are also classified based on their functional properties into either transcriptional activators (*E2F1–3a*) or repressors (*E2F3b-8*), thus creating a negative feedback loop to control the normal cell cycle. It is important to note here that the distinction between activator *E2Fs* and repressors is not finely tuned and is still subject to ongoing investigations, as in *E2F3b* for example, which has been shown to act as both a transcriptional activator as well as a repressor [49]. Naturally, due to their important role, several excellent review articles, including recent ones, have been dedicated to *E2F* family function in the cell cycle [55,66,67, 82–86], in addition to their role in specific types of cancers, such as breast [50,87,88], gastric [89] and testicular [90]. Therefore, we herein will focus on the role of E2F TFs in oral carcinogenesis specifically without delving into the overly complex and overlapping functionality of the *E2F* family in general, which can be found elsewhere. Despite that, it is important to present a short description of the positive and negative feedback loops that control the cell cycle via E2F family of TFs in order to highlight the signaling pathways involved in oral carcinogenesis.

As mentioned above, the role of E2F family of TFs is complex encompassing several aspects of cellular functions. However, when it

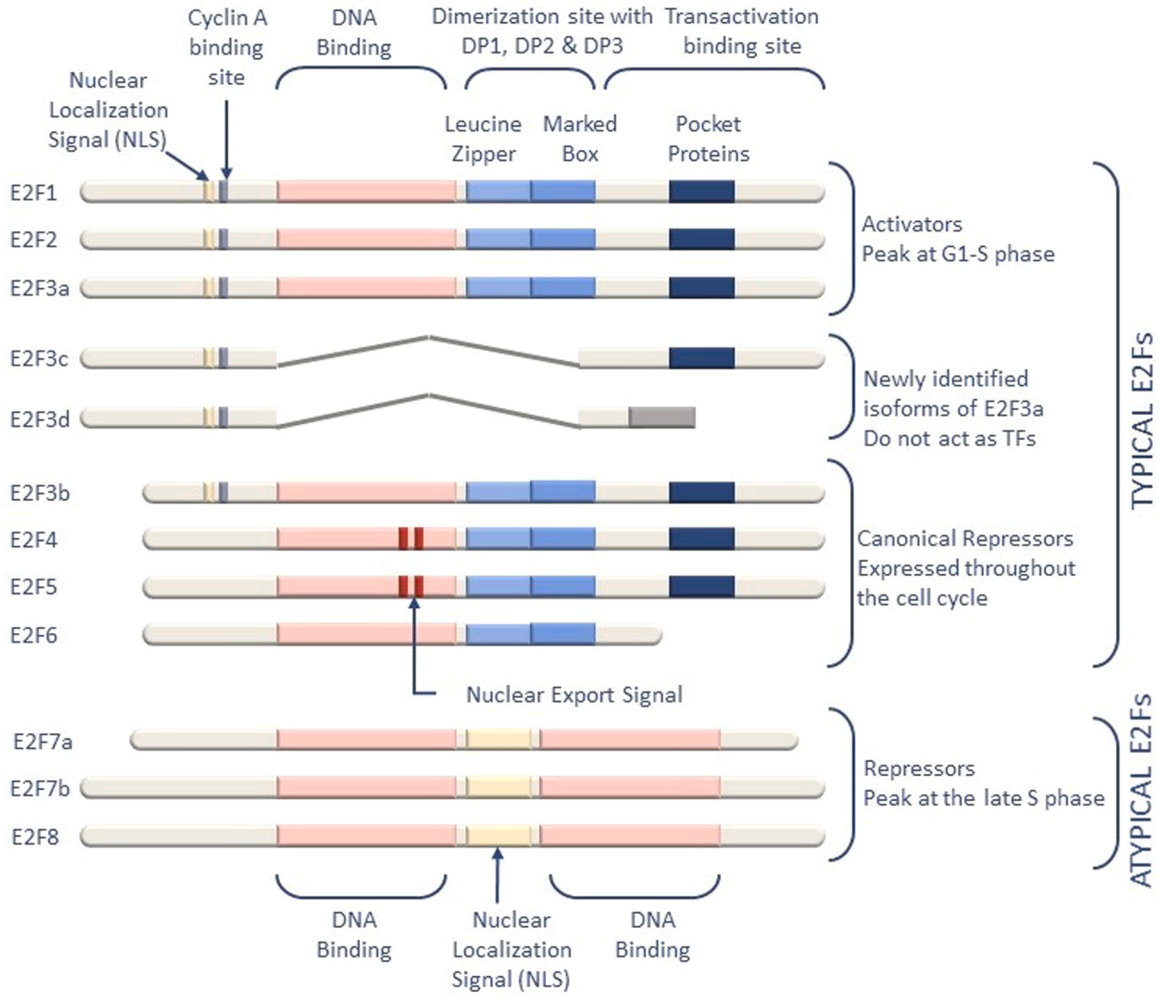

Fig. 2. ETF family structure.

comes to the cell cycle, they are mostly involved in the initiation of DNA replication enzymes and G1/S and G2/M checkpoints transition. As such, and due to the shared binding motif with *pRb* between *E2Fs* activators and repressors, (TTSSCGCC, where S= C or G), a self-regulating cycle, or feedback loop, is possible to ensure healthy cellular function [91].

In quiescent or differentiated cells (G0 phase), pocket proteins bind to *E2F*-DP heterodimers to repress their target genes. Preferential binding of different *E2F* family members to pocket proteins is observed, as Rb preferentially binds to activators, *E2F1*, *E2F2*, *E2F3*, however, in quiescence Rb binds to the repressor *E2F3b*. While other repressors, as in *E2F4* and *E2F5*, bind to pocket proteins p107 and p130, thus forming the DREAM complex (DP, Rb-like, E2F and MuvB) as a second negative feedback loop of *E2F* activation [84–86]. Under mitogenic stimulation, *E2F* activity is initiated via the induction of *cyclin D* which in turn activates *cyclin-dependent kinases 4* and *6* (*CDK4*, *CDK6*) that phosphorylate and disable pocket proteins, dissociating repressive complexes from *E2F* [92]. Subsequently, *Rb* family phosphorylation releases *E2F4* and *E2F5* [85]. Peak *E2F* activity is observed in the mid-to-late G1 phase [93], amidst which phosphorylated and inactivated pocket proteins translocate *E2F4* and *E2F5* to the cytoplasm [94]. There is a significant increase in the transcriptional activity of *E2Fs* throughout the G1 phase, as well as *cyclin E* and *CDC6* that climaxes at the G1/S phase shift. During this phase, pRB is activated by mono-phosphorylation via *CDK4* and *CDK6*, unlike p130 [95]. However, towards the end of the G1/S phase, *cyclin E* activates *CDK2* leading to pRb hyper-phosphorylation and inactivation, creating a positive feedback loop. While, activator *E2Fs* target *E2F7* and *E2F8* genes leading to their transcription and cell cycle progression into the S phase, whereby, accumulation of these two TFs suppress *E2F1* expression, a negative feedback loop that is independent of *CDKs* [94]. According to Westendorp et al. [91], *E2F7* alone can be implicated in the suppression of 89 genes that are activated by *E2Fs* involved in DNA replication. As the S phase progresses into the G2 phase, *E2F* activity starts to decline [84,94]. This is attributed to the *F box protein cyclin F* (*CCNF*) activity that degrades E2F family activators (*E2F1–3a*) [84,96], in addition to *E2F7* activation [97]. This is combined with the role of *cyclin A/CDK2* in phosphorylating activator *E2Fs*, thereby decreasing their transcriptional activity [98,99]. While, *E2F6* inhibits transcription along with PcG proteins [76]. Once the cells enter G2 phase, *E2F4* undergoes nuclear localization; in the late G2 phase, *E2F4* further suppresses *E2F* targets [94]. Boekhout and colleagues reported that in late G2 phase, the *APC/C* and *CDH1* complex (APC/C^{CDH1}) leads to the absence of *E2F7* and *E2F8* via ubiquitination and proteasome-mediated degradation [100], thus reorganizing the E2F transcriptional drive to prepare cells to re-enter the cell cycle (G1 phase). In spite of this finely tuned cycle, several studies have shown that E2Fs stability relies on post-transcriptional regulation by multiple microRNAs (miRNAs), which can play an important role during carcinogenesis [101,102], this will be discussed in the section below.

4. Post-transcriptional regulation of E2Fs

Cumulative research in various types of cancers has shown epigenetic regulations to alter the activity of *E2Fs* and their targets [83,

103–106]. An in-vivo study in mice reported upregulated *E2F1* expression to enhance *hsa-miR-17–92* family members. Following upregulation, *hsa-miRs − 17* and *-20a* negatively target *E2F1*, thus inhibiting cell proliferation. The study indicated an *E2F1/ hsa-miR-17–92* negative feedback loop initiating palatal development by regulating mesenchymal cell proliferation and cell cycle [107]. In lung cancer cell lines, enhanced *hsa-miR-128–2* expression was found to elevate mutant p53 proteins and suppress apoptosis via *E2F5* [108]. Using a rat model for hepatocellular carcinoma, it has been shown that *hsa-miRNAs − 16a*, *-34a*, *-127* and *-200b* alter the levels of *E2F3, BCL2* and *BCL6*, further deregulating apoptosis, cell proliferation, epithelial mesenchymal transition and intercellular interaction [109]. On the contrary, *hsa-miR-195* targets *E2F3, cyclin D1* and *CDK6* to repress tumorigenesis in hepatocellular carcinoma cell lines and nude mice [110]. Furthermore, in acute myeloid leukemia cells, the authors contend that *hsa-miR-26a* targets *E2F7* to trigger cellular proliferation while blocking monocytic differentiation, thus shedding a nuanced role of *E2F7* in cell cycle progression by binding to *p21* and repressing its expression [111]. Similarly, in CD133 + glioblastoma stem cells, *hsa-miR-125b* was reported to target *E2F2* to stimulate cell proliferation, [112]. While, *hsa-miR-329* blocks human glioma cell lines proliferation by targeting *E2F1*, leading to the inhibition of Akt phosphorylation and blocking G1/S transition [113]. Although these studies indicate a significant role of epigenetic modifications in *E2Fs* regulation, further investigations are necessary to unravel the underlying mechanisms between *E2Fs* and epigenetic regulations in oral carcinogenesis.

On the other hand, a recent in vivo study using NOD/SCID mice by Jia et al. [114] reported the role of *prostate cancer-associated ncRNA transcript-1* (*lncPCAT1*) in osteogenic differentiation of periodontal ligament stem cells via the *lncPCAT1–miR-106a-5p-E2F5* feed-forward loop regulatory network. *lncPCAT1* was found to inhibit the expression of *hsa-miR-106a-5p* and target *BMP2* and *E2F5*. In turn, *E2F5* enhanced *lncPCAT1* transcription, thus forming a feed-forward loop [114]. Interestingly, analysis of 91 tissue samples collected from thyroid cancer patients revealed that the expression of *hsa-miR-153–3p* was found to suppress *E2F3* expression leading to reduction in thyroid cancer cell growth, proliferation, invasion and glycolysis [115]. Moreover, in gastric cancer tissue samples from 12 patients, targeting *E2F3* by *hsa-miR-449a* was found to trigger apoptosis and suppress cell proliferation [116]. In melanoma cell lines, while *hsa-miR-205* decreases E2F1 and E2F5 protein expression [117]; in turn, an in vivo study using a mouse model revealed that one *E2F1* target, *p73*, downregulates *hsa-miR-205* expression and is associated with poor survival [118]. Other regulatory loops are found between *E2F3* and 29 individual miRNAs; the majority of these are inhibited in cancer and can plausibly induce oncogenic *E2F* activity via *E2F3* transcripts stability [119]. On the other hand, using the Drosophila model and various cancer cell lines, it was revealed that *E2F3* can also directly target the post-transcriptional repressor complex, Pumilio [120]. Pumilio along with multiple miRNAs, are known to promote a translation block to inhibit *E2F3* leading to a conformational change in the structure of *E2F3* [121]. The absence of one or both of Pumilio regulatory elements in the 3′ untranslated region (UTR) in the truncated *E2F3* inhibits the translation block by the Pumilio complex; alteration of Pumilio expression correlates with the onset and development of several types of cancers [120,121].

The possibility of regulating E2F family members post transcriptionally using specific miRNAs is a very promising therapeutic avenue that is yet to be fully materialized to fight different types of cancers, including oral.

5. E2Fs in oral cancer

Based on the important role of the E2F family of TFs in several cellular functions, their deregulation can naturally induce the onset and development of different types of cancers. However, the exact role of E2F family members, together with their key regulatory proteins (*pRb*, *cyclins* and *p53*) in oral cancer is not completely elucidated. Fig. 3 depicts the possible pathways involved in oral tumorigenesis in relation with E2F family function. In an earlier study by Henderson et al., it has been demonstrated that *E2F1* and *p53* over-expression can individually reverse the effect of telomerase activity responsible of maintaining head and neck cancer SCC cell lines immortality, thereby inducing apoptosis [122]. On the other hand, while *pRb* mutations in oral cancer are not common, however, *pRb* suppression is well established in malignant oral epithelium and correlates with aggressive forms [123–128]. Of the limited studies reporting mutations in *pRb*, a study by Kim et al. describe loss of heterozygosity of the *Rb* gene, which is shown in various cancers, including oral; with about 17% of oral cancers carrying LOH in *Rb* [129]. This mutation is shown to sensitize tumor cells to genotoxic agents and hormonal therapies [130]. A recent study by Batta and colleagues [131] reported a novel *Rb* mutation, 2039 T > C (Ile680Thr) in oral cancer patients. While Alvi et al. described frameshift mutations in exons 19–22 of the *Rb2/p130* gene in 30% of head and neck squamous cell carcinoma cases [132]. Nevertheless, in comparison to other cancers, germline or sporadic mutations in the *Rb* gene are less frequently reported in oral cancer.

Unlike *pRb*, overexpression of *cyclin D1* due to gene amplification or chromosomal translocation [133,134] is found in several human cancers including breast, lymphomas and oral squamous cell carcinomas [135–137]. Increased *cyclin D1* expression is associated with high risk of metastasis and poor prognosis in oral cancer patients [135] which is

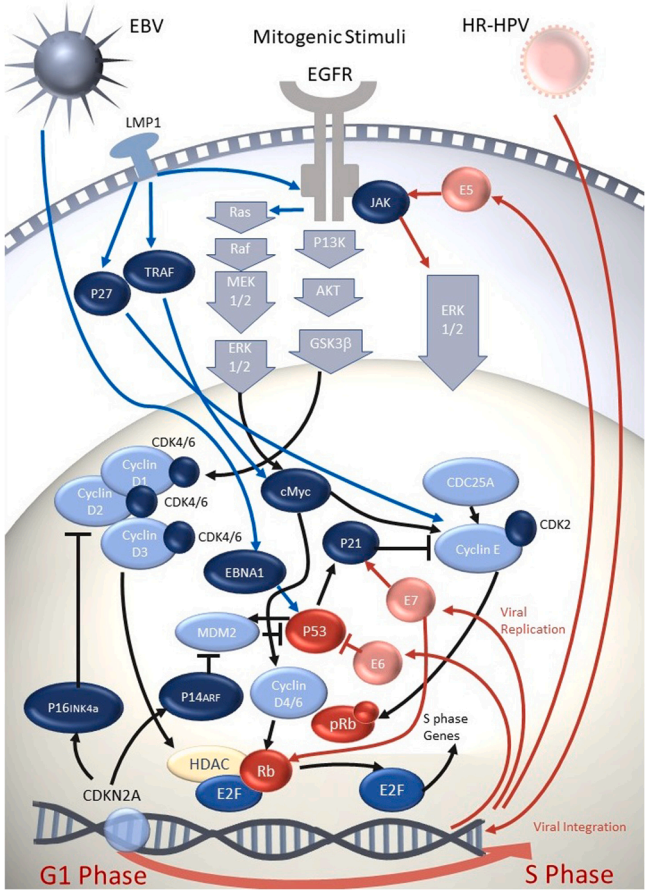

Fig. 3. Regulatory network of E2F activity representing upstream events caused by oncoproteins of high-risk HPV, EBV and mitogenic stimuli (such as UV, alcohol consumption and tobacco use) in oral carcinogenesis. The red lines represent oncoproteins of high-risk HPV interaction with different pathways leading to E2F deregulation. The blue lines reflect downstream targets of EBV oncoproteins and their crosstalk with E2F. The black lines reflect mitogenic stimuli of growth factors and their downstream cascade.

found to be associated with *p53* inactivation in vivo using transgenic mice [138]. Additionally, activation of *cyclin D1*-dependent CDKs in oral cancer is frequently induced by *CDKN2A* chromosomal alterations. Such mutations in *CDKN2A* effect its transcription of *p16*(*INK4A*) and *p14* (*ARF*) that in turn block *cyclin D1, CDK6* and *CDK4* activity during the cell cycle [139]. Thus, alterations in this important gene, which is also associated with biological aging, can induce cell cycle deregulation. Similarly, changes in *CDK6* expression were reported in oral squamous cell carcinoma cell lines, indicating a possible role of *CDK6* in inducing cell proliferation [140,141].

Additionally, a TCGA database-based analysis reported somatic mutations in *p16* in 21% of oral cancer samples [142]. While complete silencing *p16* was reported in 80% of oral cancer through point mutations, chromosomal deletion or epigenetic modifications such as promoter hypermethylation [124,127,140,141,143–149]. Therefore, loss of *p16* is considered an early event in oral carcinogenesis that is associated with poor prognosis in oral cancer patients [141,150–155].

On the other hand, *p53* is a known tumor suppressor that triggers G1 cell cycle arrest via the CDNK1A/p21/pRb/E2F1 pathway [156]. Thus, *p53* inactivation is reported in approximately 40–70% of oral squamous cell carcinomas [126,157–159] and is considered as an early event in malignant progression in younger patients [160]. Most *p53* mutations lie in the region between exons 5 and 8 of its genetic composition, which is its DNA binding domain. Additionally, since *p53* functions as a tetramer, mutations in the DNA binding domain of any one of its components disable DNA binding activity leading to a dominant negative function for the wild type product [161]. Based on the important function of *p53* in the cell cycle as a tumor suppressor, such mutations can lead to either suppression of apoptosis or cell cycle arrest, culminating in genomic instability, tumor cell survival, invasion and therapeutic resistance [162,163].

Given that all these genes are connected to the E2F family of TFs, either upstream or downstream of its functional pathway; they inevitably effect *E2F* expression in oral cancer. Notably, survival curves using Kaplan-Meier analysis reported that overexpression of the *E2F* gene correlates with worse prognosis in oral squamous cell carcinoma (OSCC) patients [164]. Nevertheless, and given the diversity of E2F TFs family functions, their role in oral carcinogenesis might be simplified by observing changes in their roles as transcriptional activators or suppressors.

5.1. Activator E2Fs in oral cancer

Of all the activators of the E2F family of TFs, *E2F1* is by far the most well studied one. Alteration in *E2F1* expression was shown to cause normal cell transformation leading to the onset of cancer [165,166]. Nevertheless, several studies reported a dual role of *E2F1* in cancer [165, 167–169]. The association between *E2F1* overexpression and oral cancers has been verified by various studies. In-silico analysis using The Cancer Genome Atlas (TCGA) that examined the methylation status of *HOX* genes in oral cancer to predict the transcription factor binding sites in this promoter reported that *HNF3α*, *E2F1*, and *SP3* are over-represented in all *HOX* gene networks, indicating a role of *HOX* genes in oral cancer via the regulation of *E2F1* [170]. Moreover, overexpression of *COX-2* and *E2F1* was reported in OSCC and oral dysplasia [171]. In OSCC, Jin and colleagues [172] reported enhanced *E2F1* to increase the expression of *Cdc7* and evade the cell cycle checkpoint resulting in uncontrolled growth and cell proliferation. Enhanced expression of *E2F1* was also confirmed in oral tongue squamous cell carcinoma (OTSCC) samples [173]. Additionally, in adenoid cystic carcinoma (ACC), the expression of several cell cycle (p53, cyclin D1, $p16^{INK4a}$, E2F1 and Ki-67) and PcG proteins were examined immunohistochemically revealing a significant increase in cell cycle proteins in ACC samples as compared to normal salivary tissue [174]. Moreover, in OSCC cell lines, overexpression of *NSD2* was found to induce *E2F1* and *YBX2* expression via *M3K36me2* histone modification, leading to inhibition of apoptosis and increased cell growth, invasion, and epithelial-mesenchymal transition [175].

However, while the overexpression of *E2F1* in oral cancers is well established, its value as a prognostic predictor is still debated, with most publications associating it with worse overall survival [176], while some correlating it with increased disease-free survival and overall survival [177]. This might be explained by differences in up/downstream signaling agents associated with this upregulation, and their responsiveness to available therapeutic options.

From an epigenetic standpoint, long non-coding RNAs (lncRNAs) have been found to effect cancer development via various TFs signaling. In OSCC, Yin et al. [178] reported that *E2F1* induces *lncRNA SNHG12* expression, which in turn induces cell proliferation, migration, invasion, and epithelial-mesenchymal transition. While, loss of *SNHG12* inhibits *E2F1* expression [178]. The authors further identified miRNAs involved in the *SNHG12/E2F1* signaling in OSCC and identified *hsa-miR-326* as the most common miRNA. Moreover, *SNHG12* and *hsa-miR-326* cooperation was found to trigger *E2F1* expression in OSCC [178].

Similar to *E2F1*, the cell cycle activator *E2F2* is also involved in tumor development and metastasis [50], however, its role as an activator is not as clear yet. This is mostly due to the various regulatory roles of *E2F2* that encompass cell differentiation, proliferation, development and apoptosis [179]. In general, overexpression of *E2F2* correlates with an enhancement of *Myc*-induced proliferation. Thus, given the significant effects of *E2F2* in cancers, Li et al. [180] proposed *E2F2* polymorphisms as potential predictive factors of oropharynx squamous cell carcinoma recurrence. A recent study evaluated the associations of five *E2F2* polymorphisms (rs6667575, rs3218121, rs3218211, rs3218148, and rs3218203) with OSCC and OPSCC and their influence on TNM staging and grading [181]. The study reported the presence of *E2F2* polymorphisms rs6667575, rs3218121, rs3218211, and rs3218148 in OSCC and OPSCC tumors, while rs3218203 did not correlate with OSCC and OPSCC [181]. Our group explored differentially expressed genes in matched primary normal and OSCC cell lines from the same patients, using cDNA microarray, we reported significant changes in the expression of 213 genes, with 91 upregulated and 122 downregulated ones [182]. Among the upregulated genes, *E2F2* was found to be 7 folds higher in cancer cells in comparison with their matched normal oral cells [182]. Contrary to these findings, another investigation showed loss of *E2F2* altered *myc* expression thereby inducing oral cavity tumorigenesis [183]. The effect of deletion of *E2F2* in OSCC was attempted to establish its role in oral carcinogenesis. This was based on an RNA sequence analysis (GSE134835) that demonstrated loss of *E2F2* due to the overexpression of the *zinc-finger protein 750* (*ZNF750*) in OSCC tissues [184]. Thus, an in-vivo investigation using nude mice xenograft model revealed that knockdown of the *ZNF750* gene enhanced the expression of *E2F2* and significantly promoted cell invasion and migration [185]; similar data were obtained in esophageal squamous cell carcinoma cells [186].

Likewise, *E2F3* is vital for cell cycle progression and differentiation, and regulates gene expressions essential for the G0/G1 to S cell cycle phase switch. A genetic study was performed by Fushimi and colleagues [187] to examine differential gene expression in OSCC cells after heavy ion beams and X-rays. Data from the study reported upregulation of *CCND1* and *E2F3* after heavy ion irradiation of OSCC, which alter their regulation of the cell cycle and induce apoptosis. However, in contrast, several studies reported that the overexpression of *E2F3* is involved in different human malignancies including HNSCC [115,116,119, 188–190]. In that regard, Zhi et al. [190], reported that *E2F3* is highly expressed in HNSCC. Notably, although studies on *E2F3* function propose that interaction between miRNAs and *E2F3* is essential to induce tumorigenesis, this is less studied in oral cancer. One exception is presented in an investigation on tongue squamous cell carcinoma (TSCC), where enhanced levels of *FOXC2-AS1* is shown to inhibit *hsa-miR-6868–5p* thereby inducing *E2F3* expression and trigger cell growth, proliferation, invasion and, metastasis [191]. Nevertheless, lack

of available data warrants an urgent need to examine the role of *E2F3* activation and its target genes on the regulatory mechanisms of oral cancers.

5.2. Repressor E2Fs in oral cancer

In comparison to studies assessing the correlation of transcriptional activators in oral cancer, those dedicated to examining the association of transcriptional repressors are scarce and warrant further investigations.

An early study by Russo and colleagues performed immunohistochemical analysis in a panel of 44 tumors of the salivary glands for the expression pattern of pRB2/p130, p107, E2F4, p27, and pCNA in addition to cytoplasmic pRb2/p130 and nuclear p107. They reported that these proteins significantly correlated with tumor grade, presence of metastasis and poor overall survival [40]. They also reported that E2F4 showed a cytoplasmic localization pattern similar to that of pRb2/p130, indicating a potential role of E2F4 and pRb2/p130 in the pathogenesis of salivary gland cancers [40]. On the other hand, Diniz et al. [192] compared 84 cell cycle genes in large (lesions >2 cm) versus small (lesions ≤2 cm) OSCC tumors by qRT-PCR. The study identified 29 downregulated genes in large tumors as compared to small ones, of which, 13 genes displayed differential expression with statistical significance. One of the identified genes in this study was *E2F4*, indicating its plausible role in early stage tumors [192].

One epigenetic study aimed to identify the miRNA signature specific for OSCC and reported downregulation of 4 miRNAs (*hsa-miR-34b*, *hsa-miR-137*, *hsa-miR-193a*, and *hsa-miR-203*) through DNA methylation. Moreover, the study reported *CDK6* and *E2F6* as potential targets of *hsa-miR-137* and *hsa-miR-193a*, respectively, indicating a role of epigenetic silencing of these miRNAs during oral carcinogenesis [193].

On the other hand, *E2F7* was found to be associated with the onset of several malignancies [194,195]. Recently, overexpression of *E2F7* was reported in OSCC cell lines by qRT-PCR as well as in OSCC tissues using the TCGA and ONCOMINE databases [196]. This was confirmed experimentally by showing that *E2F7* overexpression increased cell growth, migration and invasion via epithelial-mesenchymal transition, while silencing of *E2F7* reversed these processes [196].

As it is, E2Fs are regulated by several down/upstream targets, that create positive and negative feedback loops. Therefore, while their deregulation is evident in various cancers, it is important to differentiate the pathways responsible of such changes, which may help explain the discrepancy associated with their expression in various studies. One possible explanation can be provided by examining specific etiological agents involved in these malignancies. The following section is dedicated to examining the role of various oncogenic factors responsible of *E2F* deregulation in oral carcinogenesis.

6. Etiological factors in oral carcinogenesis and their effect on E2F family of TFs

Oral cancers have been associated with several well-known etiological factors, such as smoking, excess alcohol consumption, poor oral hygiene, and raw areca nut consumption, in addition to bacterial and viral infections. On the other hand, while widely acknowledged, biological aging is more referred to as a risk factor rather than an active agent in carcinogenesis, despite the association of most cancer cases with older age. Nevertheless, aging phenotype presents with a distinct genomic, epigenetic and systemic biological signature that cannot be ignored while studying carcinogenesis, including oral.

When it comes to viral infections, HPV is the most important agent, due to specific genetic and prognostic differences between HPV+ and HPV- cases [13]. This section is dedicated to the most prominent factors effecting oral cancer and their association with the E2F family of TFs.

6.1. HPV and E2Fs in oral cancer

Human papillomaviruses (HPVs) comprise over 450 types identified thus far, divided into high-risk and low-risk subtypes based on their association with cancer. Upon viral integration into the cell, HPV oncogenes, namely *E6* and *E7* encode oncoproteins that bind to and inactivate *p53* and *pRb*, respectively [197]. According to a study based on data from the Cancer Genome Atlas (TCGA) that compared the molecular profile of 279 head and neck squamous cell carcinomas (HNSCC) cases, HPV+ cases were found to primarily lack genetic mutations in *TP53* and *CDKN2A* as well as *CCND1* and *MYC* that are common in HPV- cases. This might be attributed to the active role of HPV oncogenes in carcinogenesis that can work independently from genetic mutations. Additionally, HPV+ cases exhibit alterations in genes encoding the *P13 kinase* pathway, *PIK3CA* mutations, *E2F1* amplification and loss of *TRAF3*, while sharing with other HNSCC types the amplification of 3q26/28 region that contains *TP63* and *SOX2* [198].

In a similar study, proteomic analysis in HPV+ and HPV- oropharyngeal carcinomas and normal epithelium revealed 2653 proteins of which 31 differentially expressed proteins were found [199]. While HPV+ tumors were enriched with proteins involved in DNA initiation and replication as well as cell cycle; enrichment analysis for transcription factor targets revealed upregulated *E2F1* expression in HPV+ tumors [199]. Similarly, another study found that the E5 oncoprotein of HPV can induce the expression of *CENPM* through *E2F1* which increases the number of cells in G2/M phase and further induces resistance to radiotherapy in HPV+ HNSCC in comparison with HPV-negative HNSCC tumors [200]. Contrary to these findings, Zhong et al. [201] reported a tumor suppressive role of *E2F1* in HPV+ oral tumors in mice. They reported higher tumor growth in HPV+ oral tumors with homozygous loss of *E2F1* as compared to tumors with heterozygous loss of *E2F1*, indicating that HPV oncogenes trigger *E2F1* pathway to inhibit oral tumor growth [201]. Thus, it is clear that HPV stimulates *E2F1*-mediated transcription via the E7-Rb-E2F1 pathway (Fig. 3).

Although uncommon, *E2F1* mutations have been reported in oral cancers in association with HPV+ cases. *E2F1*-rs3213180 polymorphism in the 3'UTR was found to alter *E2F1* gene function and disrupt the miRNA binding site [202]. This polymorphism is associated with risk of HPV-associated OSCC, particularly squamous cell carcinoma of the oropharynx (SCCOP) [203]. Additionally, *E2F1*-rs3213180 was also found to correlate with susceptibility to disease recurrence of HPV-16 + SCCOP tumors [204].

On the other hand, Li et al. [205] analyzed the correlation between HPV16 seropositivity and five *E2F2* promoter variants (rs6667575, rs3218121, rs2742976, rs3218123 and rs3218148) with SCCOP and squamous cell carcinoma of oral cavity (SCCOC) risk and found that HPV16 seropositivity was significantly associated with SCCOP risk, while each *E2F2* polymorphism alone had no significant effect on SCCOP and SCCOC risk. However, coprevalence of both HPV serological status and *E2F2* promoter variants presented significantly higher risk among SCCOP in comparison to SCCOC, indicating that risk of HPV16 + SCCOP was altered by *E2F2* promoter variants [205].

One proteomic analysis determined the global proteome of oropharyngeal carcinomas in HPV+ and HPV- cases in comparison with normal epithelium [199]. The study revealed 2653 proteins of which 31 differentially expressed proteins were chosen. HPV+ tumors were enriched with proteins involved in DNA initiation, replication and cell cycle progression as compared to HPV- tumors which included proteins involved in epithelial cell development, keratinization, and extracellular matrix organization [199]. Enrichment analysis for transcription factor targets revealed upregulated *E2F4* expression in HPV+ tumors [199].

6.2. E2F and aging

Given that the majority of cancer cases are associated with old age, thus, it is essential to take into consideration the outcome of biological

changes that accompany aging when considering the physiological conditions of cancer stemness and progression. According to the ever-growing literature on this topic, physiological changes of aging include systemic changes, as in variation in the extracellular matrix and plasma; cellular changes that represent senescence and its associated secretory phenotype; as well as genetic and epigenetic changes that are referred to by "epigenetic drift" in DNA methylation, leading to several cellular signaling deregulation.

In this regard, cellular senescence is the most studied in relation to carcinogenesis. Senescence has been previously associated with several cancers, including oral, due to their state of cell cycle arrest, via *E2Fs* repression in the G1 phase [206]. Additionally, in order to maintain a cellular growth arrest, the nutrient sensing pathway such as the mechanistic target of Rapamycin (mTOR) remains active [207], which allows these cells to re-enter an active cell cycle mode under certain conditions, as in tumorigenesis [208,209]. Senescence is mediated via the *ataxia telangiectasia-mutated* (*ATM*) kinase, which is a member of the *phosphoinositide-3 kinase like kinase* (*PIKK*). Thus, the ATM/p53/p21, and/or p16(INK4A)/pRb can be regarded as the main pathways of cellular senescence [206]. The *ATM* cascade activates *p53* and in turn *p21 (WAF1/CIP1)* leading to cell cycle arrest by persistent *Rb* activation via *CDK2* mediated inhibition of *Rb* phosphorylation. On the other hand, p16 activation inhibits *CDK4/6* thereby also effecting *Rb* function leading to persistent *E2F* repression together with its target genes necessary for the S-phase entry, thus creating a cell-cycle arrest. It is worth mentioning that while *p21(WAF1/CIP1)* induction is crucial for the initiation of senescence, however, its expression does not persist unlike that of *p16(INK4A)* which is necessary to maintain senescence [210]. With a constant state of cell cycle arrest mediated by *E2F* inactivation, the effect of senescent cells is not restricted, but spread via their tissue specific senescence associated secretory phenotype (SASP), which is heterogeneous based on the types of cells involved [211,212]. The most common components of SASP are *NF-κB* dependent pro-inflammatory factors, particularly, *IL-6* and *IL-8*, which have a major role in cancer cell immune evasion [213,214].

Although DNA methylation changes that accompany aging, or "methylation drift" and its correlation with cancer have been investigated for decades [215–217]; however, when it comes to understanding the exact relationship/causality between these two phenomena, the science is still in its infancy. This is mostly due to the belief that DNA methylation changes with aging are sporadic, just like cancer mutations. Thus, with the advent of modern proteomic and genomic screening methods, researchers were able to identify uniform DNA methylation for different types of tissues in association with biological age [218]. With this newfound knowledge cancer associated methylation pattern in relation with aging can be better understood. However, to the best of our knowledge, there is no study on the association between aging induced DNA methylation and oral cancer to date. While studies on global systemic changes associated with aging, such as circulating aging factors, on cancer are even more scarce. In a recent study, Gomes et al. studied the effect of age-associated methylmalonic acid accumulation on tumor progression [219]. This by-product of propionate metabolism was found to be significantly elevated in the serum of the older population where it may promote tumor progression by inducing SOX4 mediated transcription.

Lack of oral cancer studies under an aging phenotype is indeed a large gap in the literature, particularly given the cellular modulation changes that accompany this phenomenon which can be addressed and treated separately or in combination with well-established cancer therapeutics.

6.3. EBV and oral cancer

Epstein-Barr virus (EBV) is one of the most common oral infections worldwide. Persistent infection with EBV is associated with genetic changes that are associated with several cancers, including oral [220]. The oncoprotein of EBV, LMP1 inhibits *p27* transcription and enhances phosphorylation of *Cdk2* and *pRb* by promoting binding of *E2F4* and *p130* repressor complex at the *E2F* sites located in the *p21* promoter [221]. *EBNA3C* is reported to enhance the expression of *E2F6*, further stimulating cell cycle progression and cell growth [222].

EBV *ED-L2* promoter driven *cyclin D1* transgenic mice showed induction of dysplasia in the aero-upper digestive epithelial tissues [138, 223]. Likewise, EBV is also implicated in carcinogenesis via the E2F-Rb-HDAC complex (Fig. 3). EBV DNA polymerase promoter is triggered by *BRLF1*-induced *E2F* activity for efficient EBV lytic replication [224]; *BRLF1* promotes S phase entry by triggering the expression of *E2F1* in EBV-infected cells [225]. While the EBV early protein, *BZLF1*, is also involved in stimulating the expression of *E2F1* along with other cell cycle-associated genes in primary tonsil keratinocytes and not in normal human fibroblasts, indicating a role of *BZLF1* in promoting cell cycle progression [226]. Additionally, the EBV *BamHI-F* promoter activity is triggered by *E2F1* [227]. On the other hand, the other oncoprotein of EBV, EBNA3C, interacts with *pRB* [228,229] and stimulates loss of pRb to promote cell cycle progression and cell proliferation, indicating a role of E2F in EBV-induced malignancies [222,230].

6.4. Raw areca nut consumption

Raw areca nut (RAN) consumption is another etiological factor linked with the onset of oral, esophageal and gastric cancers [231]. In oral cancer, intake of RAN mediates *pRb*-inactivation and induces securin upregulation, a potential *E2F1* target, by altering chromatin remodeling in its promoter region leading to chromosomal instability [232].

7. Therapeutic strategies

In oral cancer, targeted therapies usually address the major signaling pathways, namely EGFR, VEGF, p13K/AKT/mTOR, AKT, c-MET, RET and others (Fig. 1). However, given the distinct disease characteristics associated with HPV+ and HPV- cancers, treatment modalities differ significantly based on the identified oncogenic factors [233]. When it comes to targeting *E2F*, HPV oncogenes *E6/E7* directly target *p53* and *pRb*, respectively, thereby deregulating the cell cycle and directly effecting *E2F* family action, therefore in these types of cancers, use of HPV vaccines can limit the effect of their oncogenes on cancer development. Studies over the last two decades have reported that suppressing *E2F* activity can block cancer cell growth and proliferation. However, given the importance of *E2F* family members in normal cellular function, strategies to single out malignant cells have been the focus of several therapeutic strategies. In general, such approaches either rely on suppressing enhanced *E2F* activity by addressing cell proliferation or by using enhanced *E2F* signature to identify and target cancer cells.

When it comes to cell proliferation, taxanes are commonly used in the treatment of a broad range of cancers, including oral. Taxanes target the cell cycle by preventing mitosis via its tubulin binding and enhanced microtubule polymerization, additionally, they phosphorylate *Bcl-2* and increase the expression of *p53* [234]. Although more than 93 taxanes have been isolated, three of them are available in the market thus far, namely: paclitaxel, docetaxel and cabazitaxel, which was only recently approved by the FDA [235]. On the other hand, two small molecules, HLM006474 (a small molecule pan-E2F inhibitor) and the nucleoside analog ly101–4B are reported to suppress *E2F* activity [236–238]. In a melanoma cell culture model, the HLM006474 molecule was shown to interact with the *E2F4-TFDP2* complex decreasing *E2F4* levels. This actions led to inhibited cell proliferation and triggered apoptosis [236]. Additionally, in an in-vitro lung cancer model, HLM006474 was tested individually and in combination with paclitaxel; the combination showed a significant effect in inhibiting proliferation [237]. On the other hand, ly101–4B was tested on pancreatic cancer cell lines and

showed efficacy only in *E2F*-highly dependent cells [238], thus indicating HLM006474 capacity to eradicate tumor cells independent of E2F activity as compared to ly101–4B which is *E2F*-dependent. Based on this information, targeted inhibition of E2F activators in combination with taxanes seems to increase the effect of *CDK4/6* inhibitors, suggesting this combination as an ideal therapeutic option (Table 1).

When it comes to targeting E2F family members in oral cancer, there are a limited number of studies. A novel *Cdc7* inhibitor, *XL413* was tested on OSCC cells individually and in combination with DNA damaging agents (cisplatin and 5-fluorouracil). The study demonstrated significant cytotoxic effects on OSCC cells and OSCC patients with high *Cdc7* expression [172]. Taking into consideration that high levels of *Cdc7* are associated with enhanced *E2F1* levels, this mini patient-derived xenografts model, support the antitumor effects of *XL413* in OSCC by blocking an *E2F1* downstream target. Notably, *XL413* did not affect non-tumor primary cells [172]. Another study reported the antitumor effects of the dormancy-inducing factor 4-hexylresorcinol (4-HR) in TSCC cells and showed loss of *E2F2* and *E2F3* expression; however, the expressions of *E2F1, E2F4, E2F5* and *E2F6* were not affected [239]. Similarly, another study evaluated the role of *COX-2* inhibitor, NS398 in a human OSCC cell line, Tca8113. The authors attributed loss of cell viability by apoptosis to tumor cell arrest at the G1 phase by inhibiting *COX-2, pRb* and *E2F1* expressions [171]. A histone deacetylase inhibitor, trichostatin A (TSA) also inhibited oral cancer cell growth and induced apoptosis by *E2F1, E2F4, HDAC1* and *p53* repression, while enhancing *Bak*, *Bax*, *cyclin E, cyclin A* and *p21* [240].

Similar to strategies used to identify therapeutic modalities targeting the E2F TFs in oral cancer, research has been carried out in other cancers as well. Some of these strategies might prove to be useful in oral cancer management based on their downstream action.

Several peptides were designed to block E2Fs binding to DNA and demonstrated efficacy in suppressing tumor cell growth [241–244]. Xie et al. [241,242] identified a seven-amino acid peptide, HHHRLSH that imitates the structure of E2F1–TFDP1 heterodimer interface structure. The peptide is coupled with penetratin (PEP) to stimulate cellular uptake and was shown to block *E2F1* transcription and *E2F*-regulated enzymes, further promoting significant cytotoxic effects in in-vitro models of Burkitt's lymphoma, small lung and prostate cancer cells [241,242]. While, encapsulation of PEP in PEGylated liposomes increases its stability in-vivo in xenograft models and significantly blocks tumor growth [241,242]. Following these studies, Shaik et al. [245] validated a secondary structure, D-Arg penetratin peptide (D-Arg PEP) an inhibitor of *E2F1* and *E2F3a* transcription. This new compound is shown to be as a more stable and aggressive solution against lung and prostate cancer cell lines, and a second-generation drug candidate for targeted molecular therapy of *E2F*-induced cancers.

Notably, a few studies reported use of mutated *E2F1* forms lacking the transactivation domain for therapeutic strategies. Bell et al. [246] demonstrated that a 75-amino acid fragment coding for the DNA binding domain of *E2F1* was adequate to trigger apoptosis. The compound had the same activity in *E2F2–3* DNA binding domains. Taking into consideration the shared DNA binding domain between various *E2F* family members, such approaches run the risk of exhibiting many unintentional outcomes in vivo. An alternative approach to target *E2F* family members can be found in a study by Garcia-Garcia et al. that presented a truncated form of *E2F1* lacking the transactivation domain. Such an approach is shown to specifically induce autophagy in human melanoma cell lines, thus presenting a potential solution against therapy-resistant tumors [247]. While, adenoviral-mediated *E2F1* gene transfer is shown to induce apoptosis both in-vitro and in-vivo in a mouse melanoma xenograft model, suggesting another potential anticancer therapeutic agent [248].

8. Conclusion

In summary, *E2Fs* play a fundamental role in regulating tumor growth, proliferation, metastasis, and drug resistance in cancers, including oral, and can be considered as stemness regulators in oral cancers. *E2Fs* are highly expressed in oral tumors and are associated with malignant progression and poor prognosis, indicating use of *E2Fs* as novel diagnostic and prognostic biomarkers. However, more work is warranted to elucidate the exact role of various *E2F* family members in oral carcinogenesis. Moreover, and given the central role of *E2Fs* in normal cellular function, more investigations using in-vivo models and

Table 1
Therapeutic strategies targeting E2F in cancers.

Compound Name	Drug Description	Target Genes	Type of Cells	Ref.
Targeting E2F in Oral Cancers				
NS398	Non-steroidal anti-inflammatory drug	**Downregulates:** Cox-2, E2F1 & pRb	OSCC cell line (Tca8113)	[171]
XL413 (synergistically with cisplatin & 5-fluorouracil)	Cdc7 inhibitor	**Downregulates:** Cdc7 expression	OSCC cell lines (HN4, HN6, HN13 & HN30) Mouse xenograft model using patient derived cells	[172]
4-HR	Dormancy-inducing factor	**Downregulates:** E2F2, E2F3 & Sp3 **Upregulates**: Sp1	TSCC cell line (SCC-9)	[239]
TSA	Histone deacetylase inhibitor	**Downregulates**: E2F1, E2F4, HDAC1, p53 & pRb **Upregulates**: p21, cyclin E, cyclin A, Bak & Bax	3 OSCC cell lines (HSC-4, Ho-1-N-1 & Ho-1-U-1) 8 Gastric Cancer Cell lines (MKN-1, −7, −28, −45 and −74 in addition to KATO III, HSC-39 & TMK-1	[240]
Targeting E2Fs in Other Types of Cancers				
HLM006474	Small-molecule E2F inhibitor	**Downregulates**: E2F4 and its targets	Melanoma cell line (A375)	[236]
(Synergistically with paclitaxel)		**Downregulates**: E2F3a, E2F3b	A panel of lung cancer cell lines (NSCLC & SCLC)	[237]
PEP	Penetratin-peptide	Inhibit E2F1 transcription	A panel of lung cancer cell lines (SCLC) & Burkitt's lymphoma cells	[241]
PEP	Penetratin-peptide encapsulated in PEGylated liposome	Downregulation of E2F1, E2F2 and E2F3	Prostate cancer cell lines (Du-145, LnCaP, PC3) Mouse xenograft model (Du-145)	[242]
D-Arg PEP	D-Arg penetration peptide encapsulated in PEGylated liposome	Inhibit E2F1 and E2F3a	Prostate cancer cell line (DU145) and lung cancer cell line (H196) Mouse xenograft model (Du-145)	[245]
AdTet-E2Ftr3	Adenovirus-mediated E2Ftr lacking E2F1 transactivation domain	Induce PARP cleavage, Decreased proenzyme Caspase-3/CPP32	Human melanoma cell lines (HEMa-LP, HS,27, SK-MEL-2, SK-MEL-28, A2058 and DM6). Human lung cancer cell lines (A549, H1299, HEK-293) Mouse xenograft model (A2058)	[248]

advanced molecular platforms are warranted to unravel the underlying complex mechanisms of *E2F* activities in normal oral versus cancer cells. Such an approach might finally elucidate potential therapeutic targets and pave the way for new treatment approaches for oral cancer.

Conflict of interest

The authors declare that there are no conflicts of interest.

Data availability

No data was used for the research described in the article.

Acknowledgments

The research work in the laboratory of Professor Ala-Eddin Al Moustafa is funded by Qatar University and QNRF grants. Open Access funding was provided by Qatar National Library.

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