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LETTER TO THE EDITOR

Malignant odontogenic tumors: epigenetics in disease and therapy

Dear editor

Odontogenic tumours are characterized by neoplastic growth arising from tooth-forming epithelial and mesenchymal tissues and involve the entire jaw (gnathic bone), commonly presenting with swelling over the jaw, dental malocclusion and misalignment. The pathology ranges from heterogeneous lesions to benign and malignant neoplasms [1]. The most frequently occurring odantomas are harmartomatous (tumour-like proliferation in the tissue) and asymptomatic, causing unerupted teeth, especially in children and adolescents. Neoplasms though rare can be aggressive and devastating involving epithelial and/or mesenchymal tissues. They are classified depending on the cells involved, into benign and malignant odontogenic carcinomas, odontogenic and non-odontogenic cysts, maxillofacial bone and cartilage tumours, osteochondromatous and giant-cell lesions and hematolymphoid tumours [2]. Odontogenic tumours pose significant challenges in their clinical management due to poor prognosis and extensive surgical and therapeutic procedures [3]. The updated WHO classification of Head and Neck tumours included ameloblastic carcinoma, primary intraosseous carcinoma, sclerosing odontogenic carcinoma, clear cell odontogenic carcinoma, ghost cell odontogenic carcinosarcoma and odontogenic sarcomas within the malignant odontogenic tumours category [4]. Regardless of the source and the tumour type, it is strongly associated with genetic factors especially dysregulation of signalling pathways, tumour suppressor gene mutations and epigenetic factors [5].

Signalling pathways effectively organize the gene expression pattern through modulation of transcription factors, cofactors and histone modifiers. The epigenetic machinery with post-translational modifications and protein-protein interactions play a dynamic role in modulating the ultimate phenotype [6]. A detailed understanding of the signalling pathways involved in the tumorigenesis process could shed light on novel biomarkers, aid targeted therapies and support pharmacologic drug discovery. The signalling network is complicated by multiple factors including pathway redundancy, crosstalks, feedback inhibition leading to reactivation of signalling control and genetic homogeneity within the tumours of different anatomical sites [7]. The cancer genome atlas program provides data on transcriptome profiling, functionally relevant nucleotide and copy number variations and DNA methylations. Such shared genomic features help chart a detailed landscape of key cascades and pathway alterations in canonical (Wnt/β-catenin) and non-canonical (Wnt/PCP or Ent/Ca^{++}) pathways associated with cancer. Mutation-induced chromatin changes in the histone post-translational modifications, modulation of nucleosome occupancy and regulation of chromatin modifiers on EGF, MSK1/2, PKCβ, JAK2-STAT5, ERK1/2, p38α, PI3K-AKT, p38 MAPK and other important signalling pathways results in dysregulation of normal regulatory functions.

The role of mutations in chromatin signalling pathways in odontogenic tumour biology remains the subject of interest. Mutation signatures in the odontogenesis-related BMP, FGF, Shh and Wnt signalling pathways reveal the tumorigenic role of BRAF mutation in ameloblastoma, KRAS in adenomatoid odontogenic tumours, PTCH1 in odontogenic keratocysts, and CTNNB1 (β-catenin) mutation in calcifying odontogenic cysts [8]. Additionally, sonic hedgehog, epidermal growth factor receptor, Akt signalling pathways and other Ras genes relate to the odontogenic tumours [9]. Recent studies evidence the role of epigenetic modifications along with genetic mutations in the development of cancers [10]. In this study, a preliminary analysis of genes associated with odontogenic tumours and a search for their interacting gene partners, CpG islands and targeting miRNAs was carried out. A search in GeneCards (Human Gene Database) with the terms 'odontogenic tumours' resulted in 502 genes. Genes that had a relevance score of more than 60 were selected and analyzed for their interacting functional partners and predicted interactions using STRING database (https://string-db.org). The number of CpG islands and the ratio of observed to expected CpGs were noted from the UCSC Genome Browser (https://genome.ucsc.edu). These CpG islands may be associated with promoter regions and are the sites of epigenetic modifications. The miRNAs targeting the genes and could potentially control the gene expression are predicted with a target score of more than 95 using miRDB online database (http://mirdb.org/) (Table 1). Oncogenes such as KIT and BRAF and tumour suppressor genes including TP53 and PTEN are well-studied for their role in tumorigenesis. The association of an increased expression of TP53 with adenomatoid odontogenic tumour has been reported [11]. Missense mutations in the tumour suppressor genes, PTEN and CDKN2A and PDGFRA [12] have been associated with calcifying epithelial odontogenic tumours. The significant role of mutations in KRAS gene in adenomatoid odontogenic tumours and MMP genes in odontogenic lesions and ameloblastoma has been reported previously [13–15], TNFSF11 has been implicated in osteopetrosis with tooth defects, their differential expression in gingival tissues and their role in the progression from periodontal disease to tumour and metastasis to the bone have been reported [16,17]. The functional enrichment analysis of protein-protein interactions provide increased coverage of associated networks and helps the discovery of novel targets for therapy [18]. A search for long noncoding RNAs associated with odontogenic tumours in Lnc2Cancer 3.0 database (http://www.bio-bigdata.com/lnc2cancer/), resulted in one (ENST00000512916) with

Table 1. Gene Hubs and miRNA predictions on odontogenic tumour-associated genes.

Gene	Gene function	Major role	Predicted functional partners with a score >0.8	Number of CpG islands	Predicted miRNAs
TP53	Cellular tumour antigen p53	Tumour suppressor	SIRT1, AURKA, DDX5, UBE3A, RPA1, MDM2, BARD1, CREBBP, EP300, CDK2	23 (1.08)	hsa-miR-3922-5p
PTEN	Phosphatase and tensin homolog	Tumour suppressor	SLC9A3R1, TP53, NEDD4, PIK3R1, DLG1, MAGI2, WWP2, PIK3CA, PTK2, PDGFRB	24 (0.91)	hsa-miR-1297; hsa-miR-5011-5p; hsa-miR-23a-3p; hsa-miR-5692c; hsa-miR-26a-5p; hsa-miR-26b-5p; hsa-miR-23c; hsa-miR-23b-3p; hsa-miR-4465; hsa-miR-5692b; hsa-miR-4775; hsa-miR-1277-5p; hsa-miR-513a-3p; hsa-miR-29c-3p; hsa-miR-29a-3p; hsa-miR-486-5p; hsa-miR-29b-3p; hsa-miR-494-3p; hsa-miR-190a-3p; hsa-miR-513c-3p; hsa-miR-32-5p; hsa-miR-30d-3p; hsa-miR-92b-3p; hsa-miR-3944-5p; hsa-miR-8485; hsa-miR-30a-3p; hsa-miR-3606-3p; hsa-miR-373-5p; hsa-miR-616-5p; hsa-miR-30e-3p; hsa-miR-92a-3p; hsa-miR-371b-5p
KIT	Mast/stem cell growth factor receptor	Cell-surface receptor for the cytokine KITLG/SCF and regulation of cell survival and proliferation, haematopoiesis	KITLG, GRB2, SH2B3, PIK3R1, EPOR, PTPN11, PTPN6, HRAS, CBL, NRAS	182 (0.84)	hsa-miR-466; hsa-miR-5011-5p; hsa-miR-4672; hsa-miR-3941
PDGFRA	Platelet-derived growth factor receptor alpha	Cell-surface receptor for PDGFA, PDGFB and PDGFC and plays an essential role in the regulation of embryonic development, cell proliferation, survival and chemotaxis.	PDGFA, PDGFB, PDGFC, CRK, PIK3R1, PDGFRB, PIK3CA, PTPN11, PLCG1, CRKL	325 (0.87)	hsa-miR-8485, hsa-miR-4719
PTCH1	Protein patched homolog 1	Tumour suppressor	CCNB1, DHH, IHH, SHH, SMO, CDON, GLI3, GAS1, ADRBK1, GLI1	401 (1.02)	hsa-let-7a-3p; hsa-miR-98-3p; hsa-let-7b-3p; hsa-let-7f-1-3p; hsa-miR-101-3p; hsa-miR-4666a-3p; hsa-miR-144-3p; hsa-miR-153-3p
TNF	Tumour necrosis factor	Stimulate cell proliferation and induce cell differentiation	TNFRSF1A, TRADD, TNFRSF1B, TRAF2, RIPK1, IKBKG, BIRC2, FADD, IL10, TNFAIP3	0	hsa-miR-5692a, hsa-miR-34a-3p
APC	Adenomatous polyposis coli protein	Tumour suppressor	AXIN1, AXIN2, ARHGEF4, GSK3B, CTNNB1, AMER1, CSNK1A1, BTRC, DLG1, DVL1	0	hsa-miR-3120-3p; hsa-miR-561-3p; hsa-miR-6853-3p; hsa-miR-5696; hsa-miR-6504-3p; hsa-miR-3942-5p; hsa-miR-582-5p; hsa-miR-10399-5p; hsa-miR-4703-5p; hsa-miR-153-3p
CDKN2A	Cyclin-dependent kinase inhibitor 2A	Tumour suppressor	CDK4, MDM2, CDK6, TP53, MYC, NPM1, CCND1, UBE2I, CCND2, HIF1A	273 (1.03)	hsa-miR-617 ((highest score of 88)
BRAF	B-raf Proto-oncogene serine/threonine-protein kinase	Mitogenic signal transduction	KRAS, MAP2K1, HRAS, NRAS, YWHAZ, MAP2K2, RAF1, IQGAP1, YWHAQ, MAPL1	90 (1.04)	hsa-miR-6507-5p; hsa-miR-12136; hsa-miR-6830-5p; hsa-miR-944; hsa-miR-302c-5p
SMARCB1	Swi/snf related, matrix associated, actin-dependent regulator of chromatin, subfamily b, member 1	Role in paediatric rhabdoid tumour	SMARCC1, SMARCD3, SMARCA2, SMARCC2, ARID1A, SMARCE1, SMARCD1, SMARCA4, ACTL6A	0	hsa-miR-4283 (highest score of 92)

miRNAs are predicted by miRdb. CpG islands were analysed from UCSC Genome Browser and the ratio of observed and expected CpG frequency is given in brackets.

apoptotic and metastatic functions associated with ameloblastoma. This long noncoding RNA is upregulated in ameloblastoma tissues and is shown to regulate cell proliferation, migration and expression of Cyclin-dependent kinase 2/4/6 and homeoboxC13 in ameloblastoma cells [19]. The COSMIC (Catalog of Somatic Mutations In Cancer) data by tissue type and histology (ameloblastoma) indicated BRAF gene with frequent mutations (62%) followed by SMO (20%), KRAS (9%) and CTNNB1 (4%) (https://cancer.sanger.ac.uk). Our preliminary bioinformatic study revealed key target genes associated with odontogenic tumours and their hub genes overlapping in the protein-protein interaction network. Further validation of predicted miRNAs and CpG islands of the target genes could provide a further understanding of the epigenetic landscape, role in cancer initiation, progression and aggression and potential use of the knowledge in effective cancer therapy. This can be achieved by the use of appropriately designed miRNA mimics, inhibitors, miRNA sponges and miRNA masking antisense oligonucleotides for tumour suppression (Figure 1).

There has been tremendous growth in studies on epigenetics and its mechanism of controlling gene expression that results in various diseases. Aberrant epigenetic alterations such as hypermethylation in the CpG islands of tumour suppressor gene promoters and hypomethylation of oncogene promoters, promote cancer onset and progression. CpG islands are the regions of DNA with a high density of cytosine–guanine dinucleotides. Mutations within the genes encoding epigenetic enzymes are related to tumorigenesis. Hypermethylation of P27 and P21 genes was observed in patients with odontogenic keratocyst [20] and P16 in ameloblastic carcinoma samples [21]. A high frequency of hypomethylation of the tumour suppressor genes P27, P53, and RB1 in odontogenic myxoma, an ectomesenchymal benign odontogenic tumour compared to the dental pulp. Studies showed increased expression of DNA methyltransferases in odontogenic keratocysts, ameloblastomas and adenomatoid odontogenic tumours indicating epigenetic activity in these tumours [22,23]. The association of DNA methyltransferase activity, histone modification H3K9ac and associated mutations with ameloblastoma [24] indicate the need for further investigations of the role of epigenetic markers in the tumorigenesis process of other odontogenic cancers.

Epigenetic modifications including DNA methylation, histone, or chromatin post-translational modifications, and long non-coding RNA regulations have a greater impact on tumorigenesis. These modifications in the gene expression without being reflected in the genomic sequence are one of the key factors in the oncogene-driven signalling pathways (Figure 1). Genetic mutations and epigenetic modifications together make cells lose homeostatic controls leading to irregulated proliferation. As epigenetic modifications are

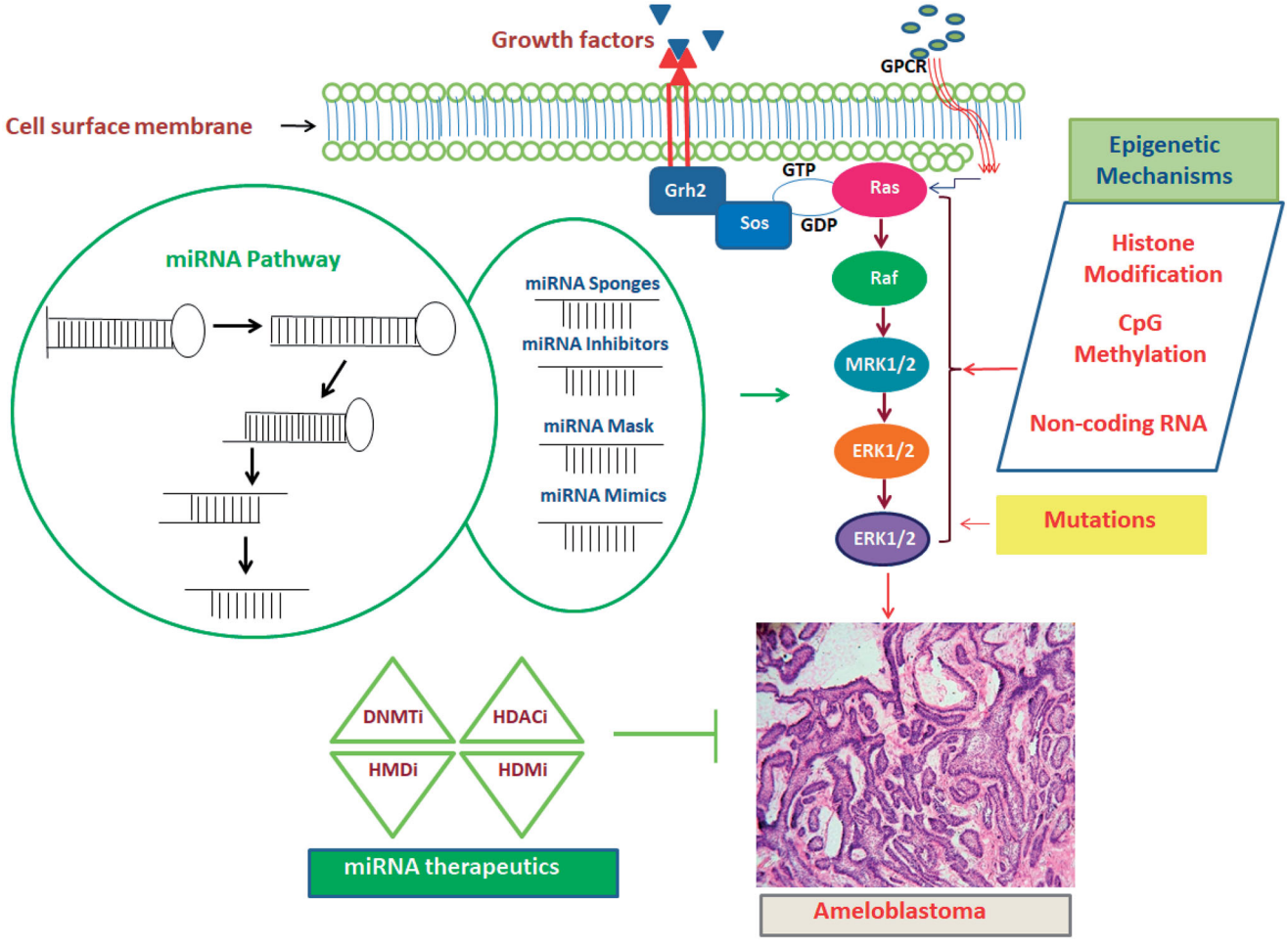

Figure 1. Functions of Epigenomics and miRNA for odontogenic tumor therapy.

reversible, application in cancer cells is envisaged as a promising therapeutic strategy and recently, epigenetics-based therapeutics is one of the emerging fields in cancer biology [25].

Protein arginine methylation, an important post-translational modification is associated with carcinoma and many other diseases. Catalyzed by the protein arginine methyltransferase (PRMT) enzyme, the proteins are involved in multiple signalling and transcription pathways, proliferation and apoptotic pathways [26]. Mammalian cells predominantly possess PRMT isoform 1 of the enzyme family and are responsible for arginine methylation [27]. Potential mutations in the PRMT1 that lead to dysregulation in the dimer formation and subsequent impairment of arginine methylation have been linked with cancers [28]. Upregulation of PRMT1 has been reported in different cancer types and found to correlate significantly with cancer grade and poor patient prognosis [29]. The role of other isoforms among the nine characterized members in higher eukaryotes namely PRMT1, PRMT2, CARM1 and PRMT7 have also been shown to add to the complexity of the understanding of its complete functional role [27]. A strong association between dysregulated PRMT expression and tumours of lung, breast, prostate, colorectal, bladder and leukaemia give convincing evidence of arginine methylation as the major driving force for many cancers [30–34]. No report exists on the role of human PRMT in odontogenic tumours. Future research on the methylation of key protein substrates could divulge interesting data on the role of PRMTs in the development, progression and aggressiveness of odontogenic tumours. In addition, the identification of "hotspot" mutations in epigenetic modifiers or epigenetic regulatory enzymes associated with tumour onset could help in the discovery of cancer inhibitors including miRNAs and lncRNAs [35]. miRNAs or microRNAs are small non-coding RNAs that have been identified as one of the vital regulatory gene families involved in epigenetic regulation [36]. The epigenetic regulation by miRNAs gives new insights and hope for the modulation of controlled gene expression in odontogenic cancer therapy [37]. miRNA signature differentially expressed in solid and unicystic ameloblastoma indicate its role as a prognostic and diagnostic tool [38] and with therapeutic importance [39]. A study on non-coding RNA expression in ameloblastoma indicated lncRNAs and small nucleolar RNA with a distinct signature of ameloblastoma [40]. Such tumour-specific RNA landscapes provide valuable information in the search for suitable diagnostic markers and therapeutic drugs.

DNA methylation inhibitors, histone deacetylases, methylases and demethylases are the potent epigenetic modulators that aid in cancer management and immunotherapies [41]. These inhibitors by reactivating the genes that were silenced by DNA methylation, reverse epigenetic modifications in most somatic cells. Although drugs that interfere with chromatin have been claimed in the 1970s, the recent emergence of genomic and proteomic sequence data availability and information on the mutations in the genes that code for proteins involved in tumorigenesis has led us to a new world of therapeutics. Agents that inhibit DNA methyltransferases and induce hypomethylation such as azacitidine and ivosidenib and histone lysine methyltransferases inhibitors such as tazemetostat, valemetostat, and histone deacetylase inhibitors vorinostat, romidepsin, belinostat, and panobinostat and some of the drugs approved by FDA for use in cancer treatments [42–44]. Most of the drugs as a combination compared to monotherapy have yielded considerable success in reverting the expression changes. However, the peril and the promise rely on epigenetic drug-induced sensitization to anti-cancer therapy. The epigenetic modifiers also induce gene expression leading to other cellular consequences compromising anti-cancer therapy. The epigenetic modifier, dacinostat (HDACi) used for breast cancer has been shown to disrupt epidermal growth factor-mediated signalling, which in turn increases metastasis and cell survival [45]. Ameloblastomas associated mutations such as MAPK signalling pathway BRAFV600E, KRAS, FGFR2 indicate the possibilities of targeted therapy. With further understanding of the mutation landscape, the efficacy of epigenetic modifying drugs at the molecular level and the epigenetic drug-induced therapy resistance in odontogenic tumours could help develop more advanced treatment strategies for better patient management.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Data availability statement

No new data was generated. All data are obtained in the UCSC genome browser and NCBI database.

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