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Histone Acetylation as a Regenerative Target in the Dentine-Pulp Complex

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If dental caries (or tooth decay) progresses without intervention, the infection will advance through the dentine leading to severe pulpal inflammation (irreversible pulpitis) and pulp death. The current management of irreversible pulpits is generally root-canal-treatment (RCT), a destructive, expensive, and often unnecessary procedure, as removal of the injurious stimulus alone creates an environment in which pulp regeneration may be possible. Current dental-restorative-materials stimulate repair non-specifically and have practical limitations; as a result, opportunities exist for the development of novel therapeutic strategies to regenerate the damaged dentine-pulp complex. Recently, epigenetic modification of DNA-associated histone 'tails' has been demonstrated to regulate the self-renewal and differentiation potential of dental-stem-cell (DSC) populations central to regenerative endodontic treatments. As a result, the activities of histone deacetylases (HDAC) are being recognised as important regulators of mineralisation in both tooth development and dental-pulp-repair processes, with HDAC-inhibition (HDACi) promoting pulp cell mineralisation *in vitro* and *in vivo*. Low concentration HDACi-application can promote de-differentiation of DSC populations and conversely, increase differentiation and accelerate mineralisation in DSC populations. Therapeutically, various HDACi solutions can release bioactive dentine-matrix-components (DMCs) from the tooth's extracellular matrix; solubilised DMCs are rich in growth factors and can stimulate regenerative processes such as angiogenesis, neurogenesis, and mineralisation. The aim of this mini-review is to discuss the role of histone-acetylation in the regulation of DSC populations, while highlighting the importance of HDAC in tooth development and dental pulp regenerative-mineralisation processes, before considering the potential therapeutic application of HDACi in targeted biomaterials to the damaged pulp to stimulate regeneration.

Keywords: histone deacetylases, dentinogenesis, regenerative endodontics, dental pulp, acetylation, histone acetyltransferases

INTRODUCTION

Dental caries (decay) is the most prevalent global non-communicable disease (WHO, 2017). The caries process initiates with a microbial biofilm forming on the tooth surface, which 'fuelled' by a dietary source of fermentable carbohydrates, ecologically shifts the plaque to an acidogenic flora, breaking down the hard tooth tissues of enamel and dentine (Nyvad et al., 2013). If the carious lesion progresses without remedial treatment, the pulp tissue in the centre of the tooth will become progressively infected and inflamed (Mjor and Tronstad, 1972; Mjor and Tronstad, 1974). The pulpal inflammation (pulpitis) provokes a robust defensive reaction with new dentine produced by the pulp's secretory cells, the odontoblasts, locally beneath the caries in a process called reactionary dentinogenesis (Smith, 2002). If the advancing caries continues until the bacteria invade the pulp tissue, odontoblast death will occur, prior to more widespread pulpal necrosis. Traditional treatment for pulp necrosis is root-canal-treatment (RCT) (**Table 1**), which effectively removes all pulp tissue; however, this is a very destructive and empirical approach. The absence of vital pulp tissue has other consequences, including removal of the tooth's developmental, reparative, and immune capacity as well as loss of the pulps proprioceptive sensors, accompanied by a significantly greater risk of fracture and tooth loss (Paphangkorakit and Osborn, 1998; Smith, 2002). The pulp; however, has considerable potential to regenerate if the insult is removed and the tooth effectively restored during vital-pulp-treatment (VPT) (Mjor and Tronstad, 1974). The damaged odontoblast layer can regenerate in a stem-cell (SC) led process, in which stem/progenitor cells cyto-differentiate under the influence of bioactive molecules released from the damaged dentine and pulp cells (Lesot et al., 1994; Smith et al., 2016; Neves et al., 2017). Unfortunately, current therapies, which aim to maintain and regenerate the pulp in VPT, are limited by low-quality hard-tissue formation and non-specific responses (Nair et al., 2008; Sangwan et al., 2013). As a result, there is significant interest in developing scientific understanding of the mechanisms that control dental SC (DSC) fate as well as identifying potential therapeutic targets to promote more effective tissue regenerative processes.

TABLE 1 | A list of abbreviations and definitions used in the text and figures.

Abbreviations	Definition
BDNF	Brain-derived neurotrophic factor
BMP	Bone morphogenetic protein
DFPC	Dental follicle progenitor cell
DMC	Dentine matrix component
DMP	Dentin matrix acidic phosphoprotein 1
DPC	Dental pulp cell
DPSC	Dental pulp stem cell
DSC	Dental stem cell
DSPP	Dentin sialophosphoprotein
ESC	Embryonic stem cell
FDA	US Food and Drug Administration
GDF-15	Growth/differentiation factor 15
GF	Growth factor
GNAT	GCN5-related *N*-acetyltransferases
HAT	Histone acetyl transferase
HDAC	Histone deacetylase
HDACi	Histone deacetylase inhibitor
LMK-235	N-[[6-(hydroxyamino)-6-oxohexyl]oxy]-3,5-dimethyl-benzamide
MMP	Matrix metalloproteinase
MYST	MOZ, YBF2/SAS3, SAS2, and TIP60
PDLC	Periodontal ligament cell
RCT	Root canal treatment
SAHA	Suberoylanilide hydroxamic acid
SC	Stem cell
TGF	Transforming growth factor
TSA	Trichostatin A
VPA	Valproic acid
VPT	Vital pulp treatment

Epigenetic modulations, DNA-methylation and histone modifications, are important regulators of DSC fate (Gopinathan et al., 2013), with histone acetylation being identified as an important regulator of bone, periodontal ligament, and dental pulp mineralisation processes as well as being a target for therapeutic inhibition (Duncan et al., 2016; Huynh et al., 2016; Ricarte et al., 2016; Cantley et al., 2017). The acetylation of DNA-associated histone (and non-histone) proteins is controlled by the enzymes histone-deacetylases (HDACs) and histone-acetyl-transferases (HATs), which alter chromatin architecture in response to cellular needs, regulating transcription (Kouzarides, 2007). HATs or lysine acetyltransferases, are bi-substrate enzymes, which are generally divided into categories of which the GCN5-Related *N*-Acetyltransferases (GNAT) and MYST families the largest, although others such as CBP/p300 may also be functionally important (Lalonde et al., 2014). HATs are further classified by their nuclear or cytoplasmic distribution (Richman et al., 1988) and have been implicated in a range of inflammatory diseases (e.g. asthma) and cancer (Ito et al., 2002; Yang, 2004). To date, HATs have not been the focus of the same level of attention as HDACs in regenerative medical or dental research and although HAT inhibitors are available, *in vitro* performance has not been replicated therapeutically (Wu et al., 2009; Lasko et al., 2017). This has been attributed to the difficulty in designing effective HAT inhibitors, as they influence a range other cellular substrates and operate as part of multi-function complexes (Wapenaar and Dekker, 2016).

There are eighteen human HDAC enzymes categorised into four separate classes, with classes I, II, and IV containing zinc-dependent enzymes (Seto and Yoshida, 2014). Class I HDACs demonstrate ubiquitous expression, while class II show tissue-specific expression and cellular localisations (Montgomery et al., 2007). The importance of class II HDAC expression in mineralising tissues has been demonstrated in bone (Ricarte et al., 2016) and teeth (Klinz et al., 2012), with the individual isoforms, -6 (Westendorf et al., 2002), -5, and -4 (Nakatani et al., 2018), highlighted as being important cellular mediators which regulate osteoblast differentiation. HDACs' roles in the regulation of mineralisation and developmental cellular processes (Gordon et al., 2015), also make them attractive therapeutic targets for pharmacological inhibition (Richon et al., 1996). Several HDAC inhibitors (HDACis), including

trichostatin A (TSA), valproic acid (VPA), and suberoylanilide hydroxamic acid (SAHA), have been shown to have clinical application in a range of diseases including cancer and inflammatory and neurodegenerative disorders (Bolden et al., 2006; Das Gupta et al., 2016; Naftelberg et al., 2017). The medical and dental literature also reports that HDACis are associated with anti-inflammatory effects, pro-mineralisation, increased SC differentiation, and overall improved regenerative responses (Halili et al., 2009; Xu et al., 2009; Wang et al., 2010; Duncan et al., 2013; Luo et al., 2018). Consequently, HDACis have the potential to enhance dentine regenerative processes in VPT by directly influencing DSC populations (Duncan et al., 2012; Luo et al., 2018) and indirectly, by inducing the solubilisation of dentine matrix components (DMCs) rich in growth factors (GFs) and other bioactive molecules (Smith et al., 2016; Duncan et al., 2017). An emerging role for HDACs in tooth development and regeneration presents an opportunity for HDACi use in novel dental regenerative materials.

The following section of this mini-review is to discuss specifically the role of histone-acetylation in the regulation of DSC populations, while highlighting the importance of HDAC in tooth development (primary dentinogenesis) and dental pulp regenerative-mineralisation processes (tertiary dentinogenesis). Finally, the therapeutic regenerative potential of a topically applied HDACi as part of next-generation dental biomaterials to regenerate the damaged pulp is considered.

REVIEW

The Need to Regenerate Dental Pulp Tissue

The tooth consists of the outermost enamel and inner dentine, which surround a centrally-placed connective tissue called the pulp. Enamel is a highly mineralised tissue produced by the ameloblast cell during tooth development; however, after eruption, enamel has no cellular capacity to continue development, repair, or regenerate. Dentine is formed by the secretory odontoblast cells, which reside at the interface between dentine and pulp, linking the two tissues in a structure that is known as the dentine-pulp-complex (Pashley, 1996). Primary dentine forms during tooth development; however, unlike enamel, secondary dentine continues to form throughout the life of the tooth and furthermore the tooth can repair damaged tissue by forming tertiary dentine in response to injurious stimuli, including caries or tooth wear (Lesot et al., 1994; Smith, 2002). There are two types of tertiary dentine, with reactionary dentine formed in response to mild to moderate irritation due to the upregulation of existing primary odontoblast activity and reparative dentine generated when severe irritation leads to odontoblast death followed by the regeneration of a new layer of odontoblast-like cells from SCs (Lesot et al., 1994).

The origin of the progenitor cells in reparative dentinogenesis is mesenchymal (Simon and Smith, 2014). Attributed to SC populations within the pulp (e.g. dental-pulp-SCs [DPSCs]) (Smith and Lesot, 2001), SCs migrating from outside the tooth (Feng et al., 2011; Frozoni et al., 2012) or undifferentiated mesenchymal cells from cell-rich and central pulp perivascular regions (e.g. pericytes) (Fitzgerald et al., 1990; Machado et al., 2016). DPSCs, reportedly account for between 1 and 5% of total permanent pulpal cells (Gronthos et al., 2000) and reside in perivascular areas potentially enabling their mobilisation to wound sites (Shi and Gronthos, 2003; Crisan et al., 2008; Casagrande et al., 2011). The dentine stores a plethora of bioactive DMCs including GFs, chemokines, bioactive-proteins, tissue proteases, and other mobilisation factors, which are released by the caries process and orchestrate healing contributing to regenerative process in the tooth (Smith, 2003; Smith et al., 2016; Duncan et al., 2017; Tomson et al., 2017). Certain dental materials exhibit the ability to solubilise DMCs and influence the quality of the new mineral tissue formed, with the outcome of VPT dependent on the dental biomaterial placed in contact with the pulp (Nair et al., 2008). Notably, calcium-silicate materials, such as mineral-trioxide-aggregate have now superseded calcium hydroxide (Bjorndal et al., 2017) as the VPT material of choice (Hilton et al., 2013). However, all current materials are limited by low-quality tertiary dentine formation, non-specific actions, and the absence of targeted components focused on tissue regenerative strategies (Duncan et al., 2011).

Regeneration processes within the dentine-pulp-complex require the presence of vital pulp tissue; however, if the inflammatory process is allowed to continue without treatment, pulp necrosis results. Regenerative endodontic efforts to avoid RCT and 'regrow' the dental pulp using either a SC-based (Iohara et al., 2011) or cell-homing (Shimizu et al., 2012) technique have demonstrated that pulpal regeneration is possible. DPSCs can be transplanted *in vivo* with a scaffold to form a new physiologically functioning pulp tissue (Nakashima et al., 2017) and although, development is hampered by expense, risk of immune-rejection, ethics, and other regulatory issues (Kim et al., 2013) these therapies have proceeded to clinical trial stage (Nakashima and Iohara, 2017). In an alternative revitalisation procedure, a decellularised or synthetic scaffold containing bioactive molecules such as GFs, pharmacological inhibitors, and mobilisation factors is placed into the root canal and endogenous SCs are 'homed' into the space before undergoing differentiation (Galler, 2016). Although, revitalisation can successfully develop a biological pulp replacement, current protocols do not specifically regenerate the odontoblast layer or indeed enable further tooth root growth, which may be necessary in under developed teeth (Shimizu et al., 2013; Eramo et al., 2018).

There is significant need to develop regenerative endodontic techniques by developing our understanding of the epigenetic processes, which control the fate and the odontogenic potential of various SC populations (Gopinathan et al., 2013; Ching et al., 2017). Histone acetylation is an obvious focus, playing a critical role in a wide range of biological processes including inflammation, mineralised tissue formation, and SC regulation, (Schroeder and Westendorf, 2005; Shuttleworth et al., 2010; Jamaladdin et al., 2014) and can be targeted by HDACi, potentially benefiting the regenerative response within VPT (de Boer et al., 2006; Duncan et al., 2016).

Histone Acetylation Regulation of Regenerative Mineralisation Processes

The nucleosome consists of tightly-coiled DNA, wrapped around a histone core. The core contains an octamer of histone proteins (H2A, H2B, H3, and H4), each with a positively charged N-terminal tail (Biswas et al., 2011). These tails extend from the core structure, facilitating post-translational modification by acetylation, methylation, phosphorylation, ubiquitination, and SUMOylation (Zhang and Reinberg, 2001). Histone acetylation generates an architecturally open chromatin structure, which is transcriptionally active, while deacetylation tightens the DNA-histone association and represses gene expression (Verdone et al., 2005). The enzymes, HAT and HDAC, mediate these processes. Histone modifications, in contrast to DNA-methylation, are highly labile, presenting attractive targets for therapeutic intervention (Kelly et al., 2010).

Notably altered HDAC expression occurs during osteogenesis (Westendorf et al., 2002; Schroeder et al., 2004), dentinogenesis (Klinz et al., 2012), and cementogenesis (Huynh et al., 2016) in a tissue-specific manner. Class I and II HDAC expression analysed in human tooth periodontal ligament cell (PDLC) cultures demonstrated that all of the five HDACs studied (HDAC-1 to -4 and -6) were highly expressed, although HDAC3 was downregulated during osteogenic differentiation (Huynh et al., 2016). Furthermore, a dental pulp study analysing extracted adult human molar teeth demonstrated that HDAC-2 and -9 were expressed in DPC, and exhibited a relatively strong expression in odontoblasts, while HDAC-1, -3, and -4 were relatively weakly expressed within the pulp tissue (Klinz et al., 2012). In the developing tooth, the role of histone methylation and demethylation has been studied (Zheng et al., 2014; Yi et al., 2016); however, currently little is known about the influence of acetylation in this process. Several studies have investigated the importance of HDACs in pulpal mineralisation processes and odontoblast differentiation *in vitro* (Duncan et al., 2012; Duncan et al., 2013; Paino et al., 2014), but further work is required to understand HDACs role during tooth development *in vivo*. Deletion of HDAC-4 in mice inhibited bone resorption and reduced thickness and cortical bone mass (Nakatani et al., 2016), and had the additional effect of inhibiting MMP-13 and *Sost/sclerostin* expression (Nakatani et al., 2018). Dentally, a mouse model of HDAC-4 KO demonstrated altered mineralisation in the roots of developing teeth (Ono et al., 2016) and the volume of enamel and dentine (**Figure 1A**). Other histological work has highlighted strong expression of another class II HDAC, -5, in the odontoblasts of developing teeth (**Figure 1B**). Supplementing DPSC cultures with HDACi has also indicated the importance of HDAC-3 downregulation during odontoblast differentiation (Jin et al., 2013), while HDAC-2 silencing in DPSCs promoted matrix mineralisation and related gene expression (Paino et al., 2014).

HDAC and HAT activity preserves the self-renewal capabilities of mesenchymal SCs (Romagnani et al., 2007; Lee et al., 2009; Jamaladdin et al., 2014) by maintaining expression of key pluripotent transcription factors, which are required to enable an open chromatin structure characteristic of embryonic SC (ESC) populations (Jamaladdin et al., 2014). Dental pulp tissue in adult teeth contains a characterised post-natal SC population of DPSCs (Gronthos et al., 2000) and as a result, modulators of SC behaviour have attracted significant interest in dentistry with suggestions that dental developmental anomalies, including dentine dysplasia and dentinogenesis imperfecta, may be related to dysregulated epigenetic modifications present during odontoblast differentiation (Sun et al., 2015). Epigenetic modifications and related differentiation profiles of two dental SC populations, DPSCs and dental follicle progenitor cells (DFPCs), were compared *via* the analysis of odontogenic gene expression including dentine sialophosphoprotein (DSPP) and dentin matrix acidic phosphoprotein 1 (DMP-1) (Gopinathan et al., 2013). Transcript levels were epigenetically-suppressed in DFPCs, while osteogenic stimulation *in vitro* demonstrated significant mineralisation increases only in DPSCs (Gopinathan et al., 2013). Notably, a highly dynamic histone modification response was demonstrated in mineralising DFPCs, but not in DPSCs, with the latter also expressing relatively high levels of the pluripotency-associated transcripts, *Oct4* and *Nanog*. It was concluded that these two neural crest-derived SC populations were distinguished by epigenetic repression of dentinogenic genes with dynamic histone enrichment in DFPCs during mineralisation. This study highlighted the potential important role of epigenetic control in odontoblasts.

HDAC role in modulation of immune and inflammatory responses are also emerging (Leoni et al., 2002; Shanmugam and Sethi, 2013; Das Gupta et al., 2016), as well as, their role in angiogenesis (Mahpatra et al., 2010; Tsou et al., 2016) and neurogenesis (Cho and Cavalli, 2014), which are critical to the promotion of regenerative processes in the dental pulp. Together, these studies highlight that HDACs are involved in range of cellular events associated with the regeneration of dentine-pulp complex, suggesting their potential roles as therapeutic targets for VPT.

HDACi in Regenerative Endodontic Therapies

HDACis chemically include short-chain fatty acids, hydroxamic acids, cyclic peptides, and benzamides (Dokmanovic et al., 2007; Marks and Xu, 2009; Yusoff et al., 2019). VPA is a short-chain fatty acid that weakly inhibits class I and IIa HDACs, while the common hydroxamic-acid-based HDACis target classes I and II HDACs. HDACi are prime discovery targets for introduction into clinical trials including SAHA (Richon et al., 1998), also known as Vorinostat, being the first HDACi to obtain US FDA-approval in 2006 for treatment of lymphoma (Grant et al., 2007). Although HDACs are critical to the control of transcription, less than 5% of expressed genes are altered by low-dose HDACi in primary DPC cultures (Duncan et al., 2016).

Pharmacological inhibition of HDACs can modulate dental-derived SC populations and promote odontoblast-like cell differentiation and mineralised tissue formation (Kwon et al., 2012; Duncan et al., 2013; Paino et al., 2014). Application of pan-HDACi, TSA, VPA, and SAHA, to rodent and human DPSC cultures enhanced mineralisation, accompanied by an

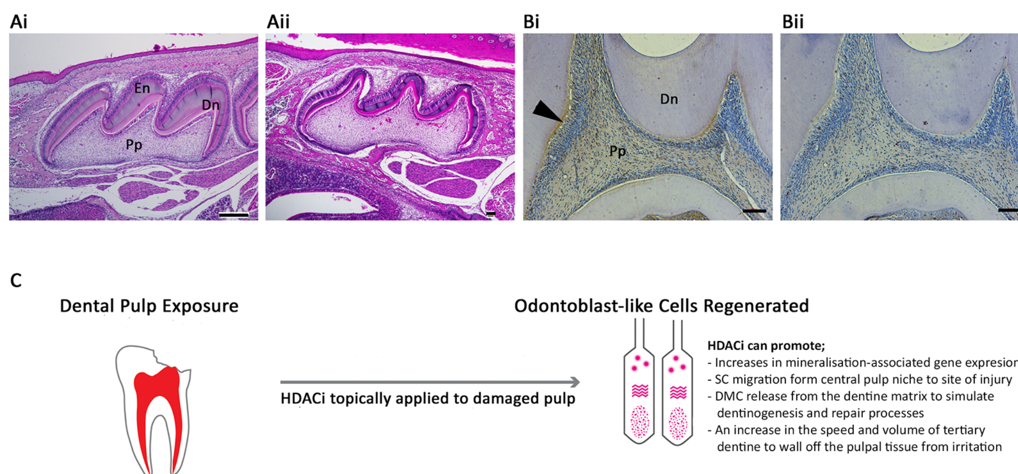

FIGURE 1 | Histone acetylation as a potential therapeutic target within the dentine-pulp complex. **(A)** Morphological comparison of post-natal day 10 maxillary first molar teeth of (Ai) WT and **(Aii)** HDAC4–/– mice using haematoxylin and eosin staining of sagittal sections highlighting differences in the volume of dentine and enamel deposited in the crown of the tooth. **(Bi)** Immunohistochemical analysis demonstrating HDAC-5 expression was evident in the odontoblasts (arrow), predentine layer, and pulp of WT adult first molar teeth in rats compared with **(Bii)** negative control. Dn = mineralised dentine; En = enamel; Pp = pulp tissue. Scale bars = **(Ai)** 250 μm, **(Aii)** 10 μm (original magnification x4), **(Bi-ii)** 50 μm (original magnification x10) (Duncan, 2017) **(C)** Schematic illustration of the potential of HDACi to be applied topically to damaged pulp tissue in a dental procedure to promote regenerative responses in VPT. Odontoblast-like cells are a replacement secretory cell after the death of primary odontoblast cells, which have been lost during the traumatic or carious insult. The differentiation of this cell type is crucial to the regeneration of dentine and mineralised tissue within the dentine-pulp complex. HDACi have been shown to augment several cellular processes central to this regenerative process, including increasing odontogenic gene expression, stimulating stem cell migration, promoting the release of bioactive dentine matrix components and accelerating mineralisation. SC, stem cell; DMC, dentine matrix component.

upregulation of genes associated with odontoblast differentiation and mineralisation, including *TGF-β1*, bone morphogenic proteins (BMPs), *DMP*, and *DSPP* (Duncan et al., 2012; Duncan et al., 2013; Paino et al., 2014; Duncan et al., 2016). In contrast to the general upregulation of mineralisation-associated transcripts, the expression of the bone metabolism marker osteocalcin was reduced, a result attributed to the use of VPA (Jin et al., 2013; Paino et al., 2014). HDACis reduced cell proliferation and viability at relatively high doses, but at lower doses did not show cytotoxic or anti-proliferative effects (Duncan et al., 2013; Paino et al., 2014; Duncan et al., 2017). SAHA was also shown to promote other reparative processes in DPC populations, including cell migration (Duncan et al., 2016; Luo et al., 2018) and cell adhesion (Luo et al., 2018). In addition to the direct regulation of SCs, HDACis also induce bioactive DMC release from dentine (Duncan et al., 2017). Bioactive molecules 'fossilised' within the dentine matrix (Cassidy et al., 1997; Smith, 2003; Grando Mattuella et al., 2007), can be released by caries, trauma, or by dental materials (Graham et al., 2006; Tomson et al., 2007). Released DMCs regulate the cyto-differentiation of progenitor cells and subsequent reparative dentine formation with bioactive components including BMPs and other GFs (Smith et al., 2016). Three HDACis, SAHA, TSA, and VPA, extracted a range of GFs from dentine, less efficiently than the well-characterised extractant EDTA for certain GFs (e.g. TGF-β1), but more effectively for others (e.g. Growth/differentiation factor 15 [GDF-15], Brain-derived neurotrophic-factor [BDNF]), while interestingly each HDACi exhibited a different extraction profile (Duncan et al., 2017). Furthermore, an *in vivo* study analysed the development of the dentine-pulp complex after systemic injection of TSA into prenatal mice and highlighted an increase in odontoblast numbers and dentine thickness compared with control specimens (Jin et al., 2013).

Currently, most research in medicine and dentistry employs pan-inhibitors; however, isoform-specific HDACis have been developed (Khan et al., 2008; Muraglia et al., 2008). It is proposed that isoform selectivity will counteract the multiple, often opposing cellular effects of HDACs (Balasubramanian et al., 2009) and reflect tissue-dependent expression of class II HDAC enzymes in particular (Verdin et al., 2003). For example, LMK-235 selectively inhibits HDAC-4 and -5 and was reported to upregulate odontoblast differentiation from human DPSCs (Liu et al., 2018). From a therapeutic perspective, low-dose short-duration HDACi application promotes DPC regenerative processes highlighting an opportunity for its use in next-generation VPT biomaterials (Duncan et al., 2016). Ethical, regulatory, and cost-effectiveness appraisal will need to be considered and material science aspects developed in order to create a controlled delivery-mechanism for the pulp. Notably, dental biomaterials containing antibiotics are commercially available (Imazato et al., 2007; Kamocki et al., 2015). Certainly, the low-dose, topical route of administration in dentistry should reduce the likelihood of systemic side effects such as fatigue, nausea, vomiting, diarrhoea, and thrombocytopenia (Subramanian et al., 2010), which have been reported following systemic-administration of HDACis at high-dose and frequency for cancer therapy.

CONCLUSION

A range of HDACs are expressed in the dentine-pulp complex and pharmacologically targeting them promotes a range of regenerative processes in DPC populations. Acetylation is central to orchestrating the differentiation and de-differentiation potential of DPSCs and understanding the intricacies of this control is crucial to enable pulpal regenerative responses as well as for designing novel therapeutic solutions. Further translational research is required to address clinical application and safety concerns in combination with scientific research to understand the mechanisms of epigenetic regulation of DPSC populations.

AUTHOR CONTRIBUTIONS

YY searched the literature, wrote and edited the manuscript. PC and AS provided guidance and edited the manuscript. ES and YK provided guidance, contributed to the figures and edited the manuscript. HD planned, provided guidance, wrote sections, contributed to the figures and edited the manuscript.

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REFERENCES

Balasubramanian, S., Verner, E., and Buggy, J. J. (2009). Isoform-specific histone deacetylase inhibitors: the next step? *Cancer Lett.* 280 (2), 211–221. doi: 10.1016/j.canlet.2009.02.013

Biswas, M., Voltz, K., Smith, J. C., and Langowski, J. (2011). Role of histone tails in structural stability of the nucleosome. *PloS Comput. Biol.* 7 (12), e1002279. doi: 10.1371/journal.pcbi.1002279

Bjorndal, L., Fransson, H., Bruun, G., Markvart, M., Kjaeldgaard, M., Nasman, P., et al. (2017). Randomized clinical trials on deep carious lesions: 5-year follow-up. *J. Dent. Res.* 96 (7), 747–753. doi: 10.1177/0022034517702620

Bolden, J. E., Peart, M. J., and Johnstone, R. W. (2006). Anticancer activities of histone deacetylase inhibitors. *Nat. Rev. Drug Discovery* 5 (9), 769–784. doi: 10.1038/nrd2133

Cantley, M. D., Zannettino, A. C. W., Bartold, P. M., Fairlie, D. P., and Haynes, D. R. (2017). Histone deacetylases (HDAC) in physiological and pathological bone remodelling. *Bone* 95, 162–174. doi: 10.1016/j.bone.2016.11.028

Casagrande, L., Cordeiro, M. M., Nor, S. A., and Nor, J. E. (2011). Dental pulp stem cells in regenerative dentistry. *Odontology* 99 (1), 1–7. doi: 10.1007/s10266-010-0154-z

Cassidy, N., Fahey, M., Prime, S. S., and Smith, A. J. (1997). Comparative analysis of transforming growth factor-beta isoforms 1-3 in human and rabbit dentine matrices. *Arch. Biol.* 42 (3), 219–223. doi: 10.1016/S0003-9969(96)00115-X

Ching, H. S., Luddin, N., Rahman, I. A., and Ponnuraj, K. T. (2017). Expression of odontogenic and osteogenic markers in DPSCs and SHED: a review. *Curr. Stem Cell Res. Ther.* 12 (1), 71–79. doi: 10.2174/1574888X11666160815095733

Cho, Y., and Cavalli, V. (2014). HDAC signaling in neuronal development and axon regeneration. *Curr. Opin. Neurobiol.* 27, 118–126. doi: 10.1016/j.conb.2014.03.008

Crisan, M., Yap, S., Casteilla, L., Chen, C. W., Corselli, M., Park, T. S., et al. (2008). A perivascular origin for mesenchymal stem cells in multiple human organs. *Cell Stem Cell* 3 (3), 301–313. doi: 10.1016/j.stem.2008.07.003

Das Gupta, K., Shakespear, M. R., Iyer, A., Fairlie, D. P., and Sweet, M. J. (2016). Histone deacetylases in monocyte/macrophage development, activation and metabolism: refining HDAC targets for inflammatory and infectious diseases. *Clin. Transl. Immunol.* 5 (1), e62. doi: 10.1038/cti.2015.46

de Boer, J., Licht, R., Bongers, M., van der Klundert, T., Arends, R., and van Blitterswijk, C. (2006). Inhibition of histone acetylation as a tool in bone tissue engineering. *Tissue Eng.* 12 (10), 2927–2937. doi: 10.1089/ten.2006.12.2927

Dokmanovic, M., Clarke, C., and Marks, P. A. (2007). Histone deacetylase inhibitors: overview and perspectives. *Mol. Cancer Res.* 5 (10), 981–989. doi: 10.1158/1541-7786.MCR-07-0324

Duncan, H. F., Smith, A. J., Fleming, G. J., and Cooper, P. R. (2011). HDACi: cellular effects, opportunities for restorative dentistry. *J. Dent. Res.* 90 (12), 1377–1388. doi: 10.1177/0022034511406919

Duncan, H. F., Smith, A. J., Fleming, G. J., and Cooper, P. R. (2012). Histone deacetylase inhibitors induced differentiation and accelerated mineralization of pulp-derived cells. *J. Endod.* 38 (3), 339–345. doi: 10.1016/j.joen.2011.12.014

Duncan, H. F., Smith, A. J., Fleming, G. J., and Cooper, P. R. (2013). Histone deacetylase inhibitors epigenetically promote reparative events in primary dental pulp cells. *Exp. Cell Res.* 319 (10), 1534–1543. doi: 10.1016/j.yexcr.2013.02.022

Duncan, H. F., Smith, A. J., Fleming, G. J., Partridge, N. C., Shimizu, E., Moran, G. P., et al. (2016). The histone-deacetylase-inhibitor suberoylanilide hydroxamic acid promotes dental pulp repair mechanisms through modulation of matrix metalloproteinase-13 activity. *J. Cell Physiol.* 231 (4), 798–816. doi: 10.1002/jcp.25128

Duncan, H. F., Smith, A. J., Fleming, G. J., Reid, C., Smith, G., and Cooper, P. R. (2017). Release of bio-active dentine extracellular matrix components by histone deacetylase inhibitors (HDACi). *Int. Endod. J.* 50 (1), 24–38. doi: 10.1111/iej.12588

Duncan, H. F. (2017). *Epigenetic Approaches to the role of histone deacetylase inhibitors (HDACi) in promoting dental pulp cell repair in vitro [PhD thesis]* (Birmingham (UK): University of Birmingham).

Eramo, S., Natali, A., Pinna, R., and Milia, E. (2018). Dental pulp regeneration via cell homing. *Int. Endod. J.* 51 (4), 405–419. doi: 10.1111/iej.12868

Feng, J., Mantesso, A., De Bari, C., Nishiyama, A., and Sharpe, P. T. (2011). Dual origin of mesenchymal stem cells contributing to organ growth and repair. *Proc. Natl. Acad. Sci. U. S. A* 108 (16), 6503–6508. doi: 10.1073/pnas.1015449108

Fitzgerald, M., Chiego, D. J.Jr., and Heys, D. R. (1990). Autoradiographic analysis of odontoblast replacement following pulp exposure in primate teeth. *Arch. Biol.* 35 (9), 707–715. doi: 10.1016/0003-9969(90)90093-P

Frozoni, M., Zaia, A. A., Line, S. R., and Mina, M. (2012). Analysis of the contribution of nonresident progenitor cells and hematopoietic cells to reparative dentinogenesis using parabiosis model in mice. *J. Endod.* 38 (9), 1214–1219. doi: 10.1016/j.joen.2012.05.016

Galler, K. M. (2016). Clinical procedures for revitalization: current knowledge and considerations. *Int. Endod. J.* 49 (10), 926–936. doi: 10.1111/iej.12606

Gopinathan, G., Kolokythas, A., Luan, X., and Diekwisch, T. G. (2013). Epigenetic marks define the lineage and differentiation potential of two distinct neural crest-derived intermediate odontogenic progenitor populations. *Stem Cells Dev.* 22 (12), 1763–1778. doi: 10.1089/scd.2012.0711

Gordon, J. A. R., Stein, J. L., Westendorf, J. J., and van Wijnen, A. J. (2015). Chromatin modifiers and histone modifications in bone formation, regeneration, and therapeutic intervention for bone-related disease. *Bone* 81, 739–745. doi: 10.1016/j.bone.2015.03.011

Graham, L., Cooper, P. R., Cassidy, N., Nor, J. E., Sloan, A. J., and Smith, A. J. (2006). The effect of calcium hydroxide on solubilisation of bio-active dentine matrix components. *Biomaterials* 27 (14), 2865–2873. doi: 10.1016/j.biomaterials.2005.12.020

Grando Mattuella, L., Westphalen Bento, L., de Figueiredo, J. A., Nor, J. E., de Araujo, F. B., and Fossati, A. C. (2007). Vascular endothelial growth factor and its relationship with the dental pulp. *J. Endod.* 33 (5), 524–530. doi: 10.1016/j.joen.2007.01.003

Grant, S., Easley, C., and Kirkpatrick, P. (2007). Vorinostat. *Nat. Rev. Drug Discovery* 6 (1), 21–22. doi: 10.1038/nrd2227

Gronthos, S., Mankani, M., Brahim, J., Robey, P. G., and Shi, S. (2000). Postnatal human dental pulp stem cells (DPSCs) in vitro and in vivo. *Proc. Natl. Acad. Sci. U. S. A* 97 (25), 13625–13630. doi: 10.1073/pnas.240309797

Halili, M. A., Andrews, M. R., Sweet, M. J., and Fairlie, D. P. (2009). Histone deacetylase inhibitors in inflammatory disease. *Curr. Top. Med. Chem.* 9 (3), 309–319. doi: 10.2174/156802609788085250

Hilton, T. J., Ferracane, J. L., Mancl, L.Northwest Practice-based Research Collaborative in Evidence-based, D (2013). Comparison of CaOH with MTA for direct pulp capping: a PBRN randomized clinical trial. *J. Dent. Res.* 92 (7 Suppl), 16S–22S. doi: 10.1177/0022034513484336

Huynh, N. C., Everts, V., Pavasant, P., and Ampornaramveth, R. S. (2016). Inhibition of histone deacetylases enhances the osteogenic differentiation of human periodontal ligament cells. *J. Cell Biochem.* 117 (6), 1384–1395. doi: 10.1002/jcb.25429

Imazato, S., Tay, F. R., Kaneshiro, A. V., Takahashi, Y., and Ebisu, S. (2007). An in vivo evaluation of bonding ability of comprehensive antibacterial adhesive system incorporating MDPB. *Dent. Mater.* 23 (2), 170–176. doi: 10.1016/j.dental.2006.01.005

Iohara, K., Imabayashi, K., Ishizaka, R., Watanabe, A., Nabekura, J., Ito, M., et al. (2011). Complete pulp regeneration after pulpectomy by transplantation of CD105+ stem cells with stromal cell-derived factor-1. *Tissue Eng. Part A* 17 (15-16), 1911–1920. doi: 10.1089/ten.tea.2010.0615

Ito, K., Caramori, G., Lim, S., Oates, T., Chung, K. F., Barnes, P. J., et al. (2002). Expression and activity of histone deacetylases in human asthmatic airways. *Am. J. Respir. Crit. Care Med.* 166, 392–396. doi: 10.1073/pnas.1321330111

Jamaladdin, S., Kelly, R. D., O'Regan, L., Dovey, O. M., Hodson, G. E., Millard, C. J., et al. (2014). Histone deacetylase (HDAC) 1 and 2 are essential for accurate cell division and the pluripotency of embryonic stem cells. *Proc. Natl. Acad. Sci. U S A.* 111 (27), 9840–9845. doi: 10.1073/pnas.1321330111

Jin, H., Park, J. Y., Choi, H., and Choung, P. H. (2013). HDAC inhibitor trichostatin A promotes proliferation and odontoblast differentiation of human dental pulp stem cells. *Tissue Eng. Part A* 19 (5-6), 613–624. doi: 10.1089/ten.tea.2012.0163

Kamocki, K., Nor, J. E., and Bottino, M. C. (2015). Effects of ciprofloxacin-containing antimicrobial scaffolds on dental pulp stem cell viability-In vitro studies. *Arch. Biol.* 60 (8), 1131–1137. doi: 10.1016/j.archoralbio.2015.05.002

Kelly, T. K., De Carvalho, D. D., and Jones, P. A. (2010). Epigenetic modifications as therapeutic targets. *Nat. Biotechnol.* 28 (10), 1069–1078. doi: 10.1038/nbt.1678

Khan, N., Jeffers, M., Kumar, S., Hackett, C., Boldog, F., Khramtsov, N., et al. (2008). Determination of the class and isoform selectivity of small-molecule histone deacetylase inhibitors. *Biochem. J.* 409 (2), 581–589. doi: 10.1042/BJ20070779

Kim, S. G., Zheng, Y., Zhou, J., Chen, M., Embree, M. C., Song, K., et al. (2013). Dentin and dental pulp regeneration by the patient's endogenous cells. *Endod. Topics* 28 (1), 106–117. doi: 10.1111/etp.12037

Klinz, F. J., Korkmaz, Y., Bloch, W., Raab, W. H., and Addicks, K. (2012). Histone deacetylases 2 and 9 are coexpressed and nuclear localized in human molar odontoblasts in vivo. *Histochem. Cell Biol.* 137 (5), 697–702. doi: 10.1007/s00418-012-0920-9

Kouzarides, T. (2007). Chromatin modifications and their function. *Cell* 128 (4), 693–705. doi: 10.1016/j.cell.2007.02.005

Kwon, A., Park, H. J., Baek, K., Lee, H. L., Park, J. C., Woo, K. M., et al. (2012). Suberoylanilide hydroxamic acid enhances odontoblast differentiation. *J. Dent. Res.* 91 (5), 506–512. doi: 10.1177/0022034512443367

Lalonde, M. E., Cheng, X., and Côté, J. (2014). Histone target selection within chromatin: an exemplary case of teamwork. *Genes Dev.* 28 (10), 1029–1041. doi: 10.1101/gad.236331.113

Lasko, L. M., Jakob, C. G., Edalji, R. P., Qiu, W., Montgomery, D., and Digiammarino, E. L. (2017). Discovery of a selective catalytic p300/CBP inhibitor that targets lineage-specific tumours. *Nature* 550, 128–132. doi: 10.1038/nature24028

Lee, S., Park, J. R., Seo, M. S., Roh, K. H., Park, S. B., Hwang, J. W., et al. (2009). Histone deacetylase inhibitors decrease proliferation potential and multilineage differentiation capability of human mesenchymal stem cells. *Cell Prolif.* 42 (6), 711–720. doi: 10.1111/j.1365-2184.2009.00633.x

Leoni, F., Zaliani, A., Bertolini, G., Porro, G., Pagani, P., Pozzi, P., et al. (2002). The antitumor histone deacetylase inhibitor suberoylanilide hydroxamic acid exhibits antiinflammatory properties via suppression of cytokines. *Proc. Natl. Acad. Sci. U. S. A* 99 (5), 2995–3000. doi: 10.1073/pnas.052702999

Lesot, H., Smith, A. J., Tziafas, D., Begue-Kirn, C., Cassidy, N., and Ruch, J. V. (1994). Biologically active molecules and dental tissue repair: a comparative view of reactionary and reparative dentinogenesis with the induction of odontoblast differentiation in vitro.

Liu, Z., Chen, T., Han, Q., Chen, M., You, J., Fang, F., et al. (2018). HDAC inhibitor LMK235 promotes the odontoblast differentiation of dental pulp cells. *Mol. Med. Rep.* 17 (1), 1445–1452. doi: 10.3892/mmr.2017.8055

Luo, Z., Wang, Z., He, X., Liu, N., Liu, B., Sun, L., et al. (2018). Effects of histone deacetylase inhibitors on regenerative cell responses in human dental pulp cells. *Int. Endod. J.* 51 (7), 767–778. doi: 10.1111/iej.12779

Machado, C. V., Passos, S. T., Campos, T. M., Bernardi, L., Vilas-Boas, D. S., Nor, J. E., et al. (2016). The dental pulp stem cell niche based on aldehyde dehydrogenase 1 expression. *Int. Endod. J.* 49 (8), 755–763. doi: 10.1111/iej.12511

Mahpatra, S., Firpo, M. T., and Bacanamwo, M. (2010). Inhibition of DNA methyltransferases and histone deacetylases induces bone marrow-derived multipotent adult progenitor cells to differentiate into endothelial cells. *Ethn Dis.* 20 (1 Suppl 1), S1–60-64.

Marks, P. A., and Xu, W. S. (2009). Histone deacetylase inhibitors: potential in cancer therapy. *J. Cell Biochem.* 107 (4), 600–608. doi: 10.1002/jcb.22185

Mjor, I. A., and Tronstad, L. (1972). Experimentally induced pulpitis. *Surg. Med. Pathol.* 34 (1), 102–108. doi: 10.1016/0030-4220(72)90278-2

Mjor, I. A., and Tronstad, L. (1974). The healing of experimentally induced pulpitis. *Surg. Med. Pathol.* 38 (1), 115–121. doi: 10.1016/0030-4220(74)90322-3

Montgomery, R. L., Davis, C. A., Potthoff, M. J., Haberland, M., Fielitz, J., Qi, X., et al. (2007). Histone deacetylases 1 and 2 redundantly regulate cardiac morphogenesis, growth, and contractility. *Genes Dev.* 21 (14), 1790–1802. doi: 10.1101/gad.1563807

Muraglia, E., Altamura, S., Branca, D., Cecchetti, O., Ferrigno, F., Orsale, M. V., et al. (2008). 2-Trifluoroacetylthiophene oxadiazoles as potent and selective class II human histone deacetylase inhibitors. *Bioorg. Med. Chem. Lett.* 18 (23), 6083–6087. doi: 10.1016/j.bmcl.2008.09.076

Naftelberg, S., Ast, G., and Perlson, E. (2017). Phosphatidylserine improves axonal transport by inhibition of HDAC and has potential in treatment of neurodegenerative diseases. *Neural Regener. Res.* 12 (4), 534–537. doi: 10.4103/1673-5374.205082

Nair, P. N., Duncan, H. F., Pitt Ford, T. R., and Luder, H. U. (2008). Histological, ultrastructural and quantitative investigations on the response of healthy human pulps to experimental capping with mineral trioxide aggregate: a randomized controlled trial. *Int. Endod. J.* 41 (2), 128–150. doi: 10.1111/j.1365-2591.2007.01329.x

Nakashima, M., and Iohara, K. (2017). Recent progress in translation from bench to a pilot clinical study on total pulp regeneration. *J. Endod.* 43 (9S), S82–S86. doi: 10.1016/j.joen.2017.06.014

Nakashima, M., Iohara, K., Murakami, M., Nakamura, H., Sato, Y., Ariji, Y., et al. (2017). Pulp regeneration by transplantation of dental pulp stem cells in pulpitis: a pilot clinical study. *Stem Cell Res. Ther.* 8 (1), 61. doi: 10.1186/s13287-017-0506-5

Nakatani, T., Chen, T., and Partridge, N. C. (2016). MMP-13 is one of the critical mediators of the effect of HDAC4 deletion on the skeleton. *Bone.* 90, 142–151. doi: 10.1016/j.bone.2016.06.010

Nakatani, T., Chen, T., Johnson, J., Westendorf, J. J., and Partridge, N. C. (2018). The deletion of Hdac4 in mouse osteoblasts influences both catabolic and anabolic effects in bone. *J. Bone Miner Res.* 33 (7), 1362–1375. doi: 10.1002/jbmr.3422

Neves, V. C., Babb, R., Chandrasekaran, D., and Sharpe, P. T. (2017). Promotion of natural tooth repair by small molecule GSK3 antagonists. *Sci. Rep.* 7, 39654. doi: 10.1038/srep39654

Nyvad, B., Crielaard, W., Mira, A., Takahashi, N., and Beighton, D. (2013). Dental caries from a molecular microbiological perspective. *Caries Res.* 47 (2), 89–102. doi: 10.1159/000345367

Ono, W., Sakagami, N., Nishimori, S., Ono, N., and Kronenberg, H. M. (2016). Parathyroid hormone receptor signalling in osterix-expressing mesenchymal progenitors is essential for tooth root formation. *Nat. Commun.* 7, 11277. doi: 10.1038/ncomms11277

Paino, F., La Noce, M., Tirino, V., Naddeo, P., Desiderio, V., Pirozzi, G., et al. (2014). Histone deacetylase inhibition with valproic acid downregulates osteocalcin gene expression in human dental pulp stem cells and osteoblasts: evidence for HDAC2 involvement. *Stem Cells* 32 (1), 279–289. doi: 10.1002/stem.1544

Paphangkorakit, J., and Osborn, J. W. (1998). Discrimination of hardness by human teeth apparently not involving periodontal receptors. *Arch. Biol.* 43 (1), 1–7. doi: 10.1016/S0003-9969(97)00090-3

Pashley, D. H. (1996). Dynamics of the pulpo-dentin complex. *Crit. Rev. Biol. Med.* 7 (2), 104–133. doi: 10.1177/10454411960070020101

Ricarte, F., Nakatani, T., and Partridge, N. (2016). PTH signaling and epigenetic control of bone remodeling. *Curr. Mol. Biol. Rep.* 2 (1), 55–61. doi: 10.1007/s40610-016-0033-7

Richman, R., Chicoine, L. G., Collini, M. P., Cook, R. G., and Allis, C. D. (1988). Micronuclei and the cytoplasm of growing Tetrahymena contain a histone acetylase activity which is highly specific for free histone H4. *J. Cell Biol.* 106 (4), 1017–1026. doi: 10.1083/jcb.106.4.1017

Richon, V. M., Webb, Y., Merger, R., Sheppard, T., Jursic, B., Ngo, L., et al. (1996). Second generation hybrid polar compounds are potent inducers of transformed cell differentiation. *Proc. Natl. Acad. Sci. U. S. A* 93 (12), 5705–5708. doi: 10.1073/pnas.93.12.5705

Richon, V. M., Emiliani, S., Verdin, E., Webb, Y., Breslow, R., Rifkind, R. A., et al. (1998). A class of hybrid polar inducers of transformed cell differentiation inhibits histone deacetylases. *Proc. Natl. Acad. Sci. U. S. A* 95 (6), 3003–3007. doi: 10.1073/pnas.95.6.3003

Romagnani, P., Lasagni, L., Mazzinghi, B., Lazzeri, E., and Romagnani, S. (2007). Pharmacological modulation of stem cell function. *Curr. Med. Chem.* 14 (10), 1129–1139. doi: 10.2174/092986707780362880

Sangwan, P., Sangwan, A., Duhan, J., and Rohilla, A. (2013). Tertiary dentinogenesis with calcium hydroxide: a review of proposed mechanisms. *Int. Endod. J.* 46 (1), 3–19. doi: 10.1111/j.1365-2591.2012.02101.x

Schroeder, T. M., and Westendorf, J. J. (2005). Histone deacetylase inhibitors promote osteoblast maturation. *J. Bone Miner Res.* 20 (12), 2254–2263. doi: 10.1359/JBMR.050813

Schroeder, T. M., Kahler, R. A., Li, X., and Westendorf, J. J. (2004). Histone deacetylase 3 interacts with runx2 to repress the osteocalcin promoter and regulate osteoblast differentiation. *J. Biol. Chem.* 279 (40), 41998–42007. doi: 10.1074/jbc.M403702200

Seto, E., and Yoshida, M. (2014). Erasers of histone acetylation: the histone deacetylase enzymes. *Cold Spring Harb. Perspect. Biol.* 6 (4), a018713. doi: 10.1101/cshperspect.a018713

Shanmugam, M. K., and Sethi, G. (2013). Role of epigenetics in inflammation-associated diseases. *Subcell Biochem.* 61, 627–657. doi: 10.1007/978-94-007-4525-4_27

Shi, S., and Gronthos, S. (2003). Perivascular niche of postnatal mesenchymal stem cells in human bone marrow and dental pulp. *J. Bone Miner Res.* 18 (4), 696–704. doi: 10.1359/jbmr.2003.18.4.696

Shimizu, E., Jong, G., Partridge, N., Rosenberg, P. A., and Lin, L. M. (2012). Histologic observation of a human immature permanent tooth with irreversible pulpitis after revascularization/regeneration procedure. *J. Endod.* 38 (9), 1293–1297. doi: 10.1016/j.joen.2012.06.017

Shimizu, E., Ricucci, D., Albert, J., Alobaid, A. S., Gibbs, J. L., Huang, G. T., et al. (2013). Clinical, radiographic, and histological observation of a human immature permanent tooth with chronic apical abscess after revitalization treatment. *J. Endod.* 39 (8), 1078–1083. doi: 10.1016/j.joen.2013.04.032

Shuttleworth, S. J., Bailey, S. G., and Townsend, P. A. (2010). Histone Deacetylase inhibitors: new promise in the treatment of immune and inflammatory diseases. *Curr. Drug Targets* 11 (11), 1430–1438. doi: 10.2174/1389450111009011430

Simon, S., and Smith, A. J. (2014). Regenerative endodontics. *Br. Dent. J.* 216 (6), E13. doi: 10.1038/sj.bdj.2014.243

Smith, A. J., and Lesot, H. (2001). Induction and regulation of crown dentinogenesis: embryonic events as a template for dental tissue repair? *Crit. Rev. Biol. Med.* 12 (5), 425–437. doi: 10.1177/10454411010120050501

Smith, A. J., Duncan, H. F., Diogenes, A., Simon, S., and Cooper, P. R. (2016). Exploiting the bioactive properties of the dentin-pulp complex in regenerative endodontics. *J. Endod.* 42 (1), 47–56. doi: 10.1016/j.joen.2015.10.019

Smith, A. J. (2002). Pulpal responses to caries and dental repair. *Caries Res.* 36 (4), 223–232. doi: 10.1159/000063930

Smith, A. J. (2003). Vitality of the dentin-pulp complex in health and disease: growth factors as key mediators. *J. Dent. Educ.* 67 (6), 678–689.

Subramanian, S., Bates, S. E., Wright, J. J., Espinoza-Delgado, I., and Piekarz, R. L. (2010). Clinical toxicities of histone deacetylase inhibitors. *Pharmaceut. (Basel)* 3 (9), 2751–2767. doi: 10.3390/ph3092751

Sun, Q., Liu, H., and Chen, Z. (2015). The fine tuning role of microRNA-RNA interaction in odontoblast differentiation and disease. *Dis.* 21 (2), 142–148. doi: 10.1111/odi.12237

Tomson, P. L., Grover, L. M., Lumley, P. J., Sloan, A. J., Smith, A. J., and Cooper, P. R. (2007). Dissolution of bio-active dentine matrix components by mineral trioxide aggregate. *J. Dent.* 35 (8), 636–642. doi: 10.1016/j.jdent.2007.04.008

Tomson, P. L., Lumley, P. J., Smith, A. J., and Cooper, P. R. (2017). Growth factor release from dentine matrix by pulp-capping agents promotes pulp tissue repair-associated events. *Int. Endod. J.* 50 (3), 281–292. doi: 10.1111/iej.12624

Tsou, P. S., Wren, J. D., Amin, M. A., Schiopu, E., Fox, D. A., Khanna, D., et al. (2016). Histone Deacetylase 5 is overexpressed in scleroderma endothelial cells and impairs angiogenesis via repression of proangiogenic factors. *Arthritis Rheumatol.* 68 (12), 2975–2985. doi: 10.1002/art.39828

Verdin, E., Dequiedt, F., and Kasler, H. G. (2003). Class II histone deacetylases: versatile regulators. *Trends Genet.* 19 (5), 286–293. doi: 10.1016/S0168-9525(03)00073-8

Verdone, L., Caserta, M., and Di Mauro, E. (2005). Role of histone acetylation in the control of gene expression. *Biochem. Cell Biol.* 83 (3), 344–353. doi: 10.1139/o05-041

Wang, G., Badylak, S. F., Heber-Katz, E., Braunhut, S. J., and Gudas, L. J. (2010). The effects of DNA methyltransferase inhibitors and histone deacetylase inhibitors on digit regeneration in mice. *Regener. Med.* 5 (2), 201–220. doi: 10.2217/rme.09.91

Wapenaar, H., and Dekker, F. J. (2016). Histone acetyltransferases: challenges in targeting bi-substrate enzymes. *Clin. Epigenet.* 8, 59. doi: 10.1186/s13148-016-0225-2

Westendorf, J. J., Zaidi, S. K., Cascino, J. E., Kahler, R., van Wijnen, A. J., Lian, J. B., et al. (2002). Runx2 (Cbfa1, AML-3) interacts with histone deacetylase 6 and represses the p21(CIP1/WAF1) promoter. *Mol. Cell Biol.* 22 (22), 7982–7992. doi: 10.1128/MCB.22.22.7982-7992.2002

World Health Organization (2017). Sugars and Dental Caries. Geneva, Switzerland. WHO publication no: WHO/NMH/NHD/17.12 [WWW document].

Wu, J., Xie, N., Wu, Z., Zhang, Y., and Zheng, Y. G. (2009). Bisubstrate inhibitors of the MYST HATs Esa1 and Tip60. *Bioorg. Med. Chem.* 17, 1381–1386. doi: 10.1016/j.bmc.2008.12.014

Xu, Y., Hammerick, K. E., James, A. W., Carre, A. L., Leucht, P., Giaccia, A. J., et al. (2009). Inhibition of histone deacetylase activity in reduced oxygen environment enhances the osteogenesis of mouse adipose-derived stromal cells. *Tissue Eng. Part A* 15 (12), 3697–3707. doi: 10.1089/ten.tea.2009.0213

Yang, X. (2004). The diverse superfamily of lysine acetyltransferases and their roles in leukemia and other diseases. *Nucleic Acids Res.* 32 (3), 959–976. doi: 10.1093/nar/gkh252

Yi, Q., Cao, Y., Liu, O. S., Lu, Y. Q., Wang, J. S., Wang, S. L., et al. (2016). Spatial and temporal expression of histone demethylase, Kdm2a, during murine molar development. *Biotech. Histochem.* 91 (2), 137–144. doi: 10.3109/10520295.2015.1106586

Yusoff, S. I., Roman, M., Lai, F. Y., Eagle-Hemming, B., Murphy, G. J., Kumar, T., et al. (2019). Systematic review and meta-analysis of experimental studies evaluating the organ protective effects of histone deacetylase inhibitors. *Transl. Res.* 205, 1–16. doi: 10.1016/j.trsl.2018.11.002

Zhang, Y., and Reinberg, D. (2001). Transcription regulation by histone methylation: interplay between different covalent modifications of the core histone tails. *Genes Dev.* 15 (18), 2343–2360. doi: 10.1101/gad.927301

Zheng, L. W., Zhang, B. P., Xu, R. S., Xu, X., Ye, L., and Zhou, X. D. (2014). Bivalent histone modifications during tooth development. *Int. J. Sci.* 6 (4), 205–211. doi: 10.1038/ijos.2014.60

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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