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Review

Epigenetic mechanisms in odontogenic tumors: A literature review

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ABSTRACT

Objective: Epigenetic mechanisms, such as DNA methylation, regulate important biological processes as gene expression and it was suggested that these phenomena play important roles in the carcinogenesis and tumor biology. The aim of this review is to provide the current state of knowledge about epigenetic alterations, focusing mainly on DNA methylation, reported in odontogenic tumors.

Design: Literatures were searched based in the combination of the following keywords: odontogenic tumors, epigenetics, DNA methylation, histone modifications, non-coding RNA, microRNA, DNA methyltransferases. Electronic databases (Medline/PubMed, Scopus and Web of Science) were screened.

Results: The analysis of epigenetic alterations in different tumors has rapidly increased; however, limited information is available about epigenetic mechanisms involved in the formation of odontogenic tumors. DNA methylation is the most studied epigenetic modification in these tumors and the participation of non-coding RNA's in odontogenic tumors has been recently addressed. Differential expression of DNA methyltransferases, altered DNA methylation patterns and aberrant expression of non-coding RNA's were reported in odontogenic tumors.

Conclusions: Current studies suggest epigenetics as an emerging mechanism, possibly implicated in etiopathogenesis of odontogenic tumors. Deeper understanding of the epigenetic abnormalities in these tumors could show potential applications as biomarkers or therapeutic possibilities in the future.

1. Introduction

Genetic contribution to cancer is related mainly to mutations in oncogenes and tumor suppressor genes, which cause gain or loss of function and altered gene expression. Traditionally, genetic mutations have been considered the central causes of neoplasia; however, now, disruption of epigenetic mechanisms has been included in this paradigm (You & Jones, 2012). Thus, it was suggested that genetic and epigenetic alterations influence each other and both can cooperate in initiation and progression of tumors (Shen & Laird, 2013; You & Jones, 2012). The epigenetic term is used to describe the hereditable changes that do not involve variations in the sequence in the DNA. Recently this term has been used to specify the study of the chromatin (Dawson, 2017). Similar to genetic changes, alterations in epigenetic mechanisms can induce abnormal gene expression (You & Jones, 2012). However, epigenetic modifications are dynamic and possibly reversible, indicating a potential therapeutic role to explore (Biswas & Rao, 2017).

Epigenetic phenomena include, histone modifications, expression of non-coding RNA's and methylation of DNA (You & Jones, 2012). DNA methylation on the fifth position of cytosine (5mC) is a modification associated to gene repression and activation, splicing regulation, imprinting, nucleosomes positioning and recruitment of transcription factors (Tirado-Magallanes, Rebbani, Lim, Pradhan, & Benoukraf, 2017).

In mammals, 80% of DNA methylation occurs at CpG sites; however, significant methylation at non-CpG sites (in sites CHG and CHH where H can be A, G or T) is detected in pluripotent stem cells, neuronal cells during brain development and after neurogenesis (Law & Jacobsen,

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2010; Lister et al., 2013; Ramsahoye et al., 2000; Ziller et al., 2011).

The enzymes responsible for DNA methylation are DNA methyltransferases including DNMT1, DNMT3A, DNMT3B and DNMT3C (Barau et al., 2016). During replication, DNMT1 upholds global DNA methylation and prefers hemimethylated DNA (Hermann, Goyal, & Jeltsch, 2004). De novo methylations are realized by DNMT3A and DNMT3B linked to DNMT3L (Jia, Jurkowska, Zhang, Jeltsch, & Cheng, 2007; Ooi et al., 2007). It has been reported that de novo methylation also can be performed by the DNMT3C (Barau et al., 2016). DNMT1, DNMT3A and DNMT3B are frequently overexpressed in solid neoplasms (Butcher & Rodenhiser, 2007; Ibrahim et al., 2011; Zhao et al., 2010). Mutated forms of DNMT1 and DNMT3A were detected in solid and blood malignancies, respectively (Kanai, Ushijima, Nakanishi, Sakamoto, & Hirohashi, 2003; Ley et al., 2010). Finally, DNMT1, DNMT3A and DNMT3B have also been reported to be deleted in mouse tumor model (Gao et al., 2011; Peters et al., 2013; Vasanthakumar et al., 2013).

A family of proteins called ten-eleven translocation (TET) has been reported to regulate DNA demethylation (Pastor, Aravind, & Rao, 2013). This family of proteins is constituted by TET1, TET2 y TET3 (Pastor et al., 2013). Frequent mutations or deletion of the TET2 gene have been reported in hematological malignancies (Delhommeau et al., 2009; Langemeijer et al., 2009). Unlike TET2, TET1 and TET3 are rarely mutated in hematological malignancies (Abdel-Wahab et al., 2009). In solid tumors, TET1 and TET2 have low levels of expression (Hsu et al., 2012; Lian et al., 2012; Liu et al., 2013).

It is well known that global hypomethylation is a general feature of cancer. For example, hypomethylations are associated to invasive and advanced stages in gastric cancer and it has been observed in the progression of cervical dysplasia to cervical cancer (Hoffman, 2017).

On the other hand, specific hypermethylation of the promoter and the first exon in CpG sites is a mechanism that generates gene silencing and has been associated with the development of cancer (Martinez-Banos, Sanchez-Hernandez, Jimenez, Barrera-Lumbreras, & Barrales-Benitez, 2017). Paradoxically, DNA methylation in the body of the gene is associated with gene activation and can even impact in the splicing (Lev Maor, Yearim, & Ast, 2015).

Thus, the tumor biology is profoundly influenced by the changes in the epigenome and the objective of epigenetic drugs is to reset the changes of the epigenome (Dawson, 2017). Nowadays, the most advanced epigenetic therapy in oncology uses DNMT and histone deacetylase inhibitors (Dawson, 2017).

1.1. Odontogenic tumors

The odontogenic tumors are a heterogeneous group of lesions that vary from hamartomas to benign and malign neoplasms and generally they are intraosseous. The classification of these lesions is based on the origin tissue and histological characteristics. The clinical effects of these tumors are varied, including: disfigurement, jaw extension and expansion, bone and root resorption or teeth mobility (Garg, Chandra, Raj, Fareed, & Zafar, 2015; Yukimori et al., 2017).

The exact etiology of odontogenic tumors is still not well understood. However, excellent works using next-generation sequencing have reported frequent specific mutations in odontogenic tumors (Brown et al., 2014; Kurppa et al., 2014; Sweeney et al., 2014; Yukimori et al., 2017). Moreover, the functional relevance and clinical significance of these mutations have been addressed (Brown et al., 2014; Gomes, Guimaraes, Diniz, & Gomez, 2017; Kurppa et al., 2014; Sweeney et al., 2014), supporting that genetic changes seem to be the central causes of most odontogenic tumors. For example, mutations in PTCH1 gene have been extensively analyzed in keratocystic odontogenic tumors (KOT) (Gomes et al., 2017; Guo et al., 2013). Activating mutations in Smoothened (SMO), a protein involved in the sonic hedgehog pathway, have been reported in ameloblastomas (AB) (Sweeney et al., 2014). Also, mutations in the serine-threonine kinase, BRAF in these tumors can result in activation of this enzyme, enhancing cell proliferation and survival (Brown et al., 2014; Sweeney et al., 2014).

On the other hand, reports analyzing the differential expression of DNMT's and DNA methylation of diverse genes in odontogenic tumors and more recently, non-coding RNA's, suggest epigenetics as an emerging mechanism; which could be implicated in development and progression of these entities, possibly coopering with genetic alterations as observed in other tumors and fine-tuning expression of genes involved in cell cycle, apoptosis or extracellular matrix remodeling. Even thought, the epigenetic roles in these tumors are still not fully clarified and more studies are needed to provide further deeper insights, many potential applications as biomarkers or therapeutic possibilities have been opened. The aim of this review is to provide the present knowledge about the epigenetic alterations in odontogenic tumors, focusing on changes of DNA methylation patterns. Finally, we mention other epigenetic alterations recently analyzed

2. DNA methylation in odontogenic tumors

2.1. DNA methyltransferases (DNMT's)

Expression of DNMT1, DNMT3A and DNMT3B has been analyzed in different odontogenic tumors (Gomes, Brito, Andrade, & Gomez, 2010; Guimaraes, Antunes, Duarte, Ferro, & Nunes, 2015). In those works, the nuclear expression of DNMT's was analyzed by immunohistochemistry, since nuclear localization suggests the presence of the actual functional DNMT proteins (Gomes et al., 2010; Guimaraes et al., 2015). Nuclear expression of DNMT1 was detected in ameloblastomas (AB), keratocystic odontogenic tumors (KOT), adenomatoid odontogenic tumors (AOT), calcifying cystic odontogenic tumors (CCOT), calcifying epithelial odontogenic tumors (CEOT), ameloblastic fibromas (AF), ameloblastic fibro-odontomas (AFO), central odontogenic fibromas (COF), peripheral odontogenic fibromas (POF) and odontogenic myxomas (OM) (Gomes et al., 2010; Guimaraes et al., 2015). In these same tumors, nuclear expression of DNMT3A was not detected, except for KOT and CEOT, which showed expression in 10–30% and 20% of the analyzed samples, respectively. Interestingly, cytoplasmic expression of DNMT3A was detected in all tumors, suggesting a minor role of DNMT3A in DNA methylation of odontogenic tumors, since this DNMT did not move to the nucleus to perform its function in almost all analyzed tumors (Gomes et al., 2010; Guimaraes et al., 2015). Moreover, nuclear expression of DNMT3B was detected in almost all odontogenic tumors mentioned, with exception of CCOT and OM (Guimaraes et al., 2015).

The alterations in mechanisms that regulate the expression of DNMT's in odontogenic tumors remain to be elucidated; in this sense, different mechanisms have been suggested to regulate the expression and activity of DNMT's, such as, expression of transcriptional regulators (e.g. Sp1 and Sp3 zinc finger proteins or Forkhead O transcription factor 3a protein), expression of microRNA's (miRNA's) and post-translational modifications in DNMT proteins (Lin & Wang, 2014). On the other hand, the reported higher nuclear expression of DNMT1 and DNMT3B could suggest more participation of these enzymes in DNA methylation than DNMT3A in odontogenic tumors; additionally, these observations could indicate that methylation is an important epigenetic mechanism in these tumors (Guimaraes et al., 2015). Differential expression of DNMT's could be altering the DNA methylation patterns, affecting the expression of diverse genes and contributing in the development and behavior of different odontogenic tumors.

2.2. LINE-1

Long interspersed element-1 (LINE-1) is an interspersed repetitive sequence and approximately, 500,000 copies of this element are found in the human genome. LINE-1 comprises different regions; 5′ untranslated region (5′UTR), which harbors two internal promoters, has