Brazilian Dental Science

unesp
UNIVERSIDADE ESTADUAL PAULISTA
"JÚLIO DE MESQUITA FILHO"
Instituto de Ciência e Tecnologia
Campus de São José dos Campos

ORIGINAL ARTICLE

DOI: https://doi.org/10.4322/bds.2023.e3790

Estrogen deficiency influences TNF-α and IL-1β gene expression in the odontogenic region of dental hypofunctional condition

A deficiência de estrógeno influencia a expressão gênica de TNF-α e IL-1β na região odontogênica de dentes em hipofunção

Igor Domingos dos ANJOS[1], Vinícius Otávio NOGUEIRA[1], Martinelle Ferreira da Rocha TARANTO[1], Lucas Alexandre RAMAZZOTTO[2], Paulo NELSON-FILHO[3], Erika Calvano KÜCHLER[4,5], Maria Angélica Hueb de MENEZES-OLIVEIRA[4], César Penazzo LEPRI[4], Flares BARATTO-FILHO[5,6], Isabela Ribeiro MADALENA[1,4,6]

1 - Centro Universitário Presidente Tancredo de Almeida Neves, Faculdade de Odontologia. São João del Rei, MG, Brazil.
2 - Universidade Federal de São Carlos, Escola de Biotecnologia. São Carlos, SP, Brazil
3 - Universidade de São Paulo, Faculdade de Odontologia de Ribeirão Preto, Departamento de Odontopediatria. Ribeirão Preto, SP, Brazil
4 - Universidade de Uberaba, Departamento de Biomateriais. Uberaba, MG, Brazil.
5 - Universidade Tuiuti do Paraná, Faculdade de Odontologia. Curitiba, PR, Brazil.
6 - Universidade da Região de Joinville, Departamento de Odontologia. Joinville, SC, Brazil.

How to cite: Anjos ID, Nogueira VO, Taranto MFR, Ramazzotto LA, Nelson-Filho P, Küchler EC, et al. Estrogen deficiency influences TNF-α and IL-1β gene expression in the odontogenic region of dental hypofunctional condition. Braz Dent Sci. 2023;26(2):e3790. https://doi.org/10.4322/bds.2023.e3790

ABSTRACT

Objective: Scientific evidence suggests that estrogen deficiency and genetic factors have an influence on the development of the stomatognathic system. This study aimed to evaluate the influence of estrogen deficiency on the gene expression of TNF-α, IL-1β, IL-6 and IL-10 during dental development in a murine model. **Material and Methods:** Wistar Hannover rats were divided into two groups according to the intervention received: Hypoestrogenism Group - ovariectomy surgery and Control Group - fictitious surgery. To evaluate the dental development, the lower incisor was chosen. The mandibular incisor hypofunction model was performed by incisal adjustment. The homologous incisor exerted a hyperfunction. The animals were evaluated throughout the pubertal period. After euthanasia, the hemimandibles were removed to evaluate the gene expression of the TNF-α, IL-1β, IL-6 and IL-10 in the odontogenic region of the incisors through real time PCR. Kruskal-Wallis test and Dunn's posttest were performed. The level of significance was 5%. **Results:** There were statistically significant differences of TNF-α and IL-1β gene expression between the hypoestrogenism and control groups under hypofunction condition (p=0.0084, p=0.0072, respectively). **Conclusion:** Estrogen deficiency influences TNF-α and IL-1β gene expression in the odontogenic region of the hypofunctional teeth.

KEYWORDS

Osteogenesis; Estrogen; Proinflammatory cytokines; Gene Expression; Genes.

RESUMO

Objetivo: Evidências científicas sugerem que a deficiência de estrógeno e fatores genéticos influenciam o desenvolvimento do sistema estomatognático. Este estudo teve como objetivo avaliar a influência da deficiência de estrógeno na expressão gênica de TNF-α, IL-1β, IL-6 e IL-10 durante o desenvolvimento dentário em modelo murino. **Material e Métodos:** Ratas Wistar Hannover foram divididas em dois grupos de acordo com a intervenção recebida: Grupo Hipoestrogenismo - cirurgia de ovariectomia e Grupo Controle - cirurgia fictícia. Para avaliar o desenvolvimento dentário, o incisivo inferior foi escolhido. O modelo de hipofunção dos incisivos inferiores foi realizado por ajuste incisal. O incisivo homólogo exercia hiperfunção dentária. Os animais foram avaliados durante todo o período puberal. Após a eutanásia, as hemimandíbulas foram removidas para avaliar a expressão gênica do TNF-α, IL-1β, IL-6 e IL-10 na região odontogênica dos incisivos por meio de PCR em tempo real. Foi realizado o teste de Kruskal-Wallis e o pós-teste de Dunn. O nível de significância foi de 5%. **Resultados:** Houve diferenças estatisticamente significativas na expressão gênica de TNF-α e IL-1β entre os grupos hipoestrogenismo e controle sob condição de hipofunção dentária (p=0,0084, p=0,0072, respectivamente). **Conclusão:** A deficiência de estrógeno influencia a expressão gênica de TNF-α e IL-1β na região odontogênica de dentes hipofuncionais.

PALAVRAS-CHAVE

Osteogênese; Estrogênio; Citocinas pró-inflamatórias; Expressão gênica; Genes.

INTRODUCTION

Estrogen is a steroid hormone present and active throughout an individual's life [1]. Although it is primarily responsible for female characteristics, estrogen also plays an important role in the neuroendocrine, vascular, skeletal, and immune systems of both sexes [1-3]. Recent research has attributed great value to knowledge about the molecular mechanisms that estrogen and/or its deficiency could cause in the human body [4-10]. Estrogen deficiency is observed in children through congenital conditions associated with chromosomal, gonadal, or atypical phenotype sexual development [11]. Thus, it is important to know the implications of estrogen and its deficiency in the development of the stomatognathic system. Evidence demonstrates gene overexpression of estrogen receptors (ERβ) in cells involved odontogenesis and tooth eruption process in estrogen deficiency [10]. Estrogen deficiency is capable of causing bone formation impaired by the action of tumor necrosis factor - α (TNF-α) on mesenchymal cells [12]. TNF-α can cause an increase in the expression of interleukin 1β (IL-1β) and interleukin 6 (IL-6) [13,14]. Evidence also suggests that IL-6 is the main cytokine expressed in estrogen deficiency [15]. However, interleukin 10 (IL-10) could also be shown to have an altered expression capable of inhibiting the differentiation of Th17 cells, generating the regression of osteoclastogenesis in the murine model [16].

Dental development is an important event for the harmonious development of the stomatognathic system and, consequently, homeostasis of general health [17,18]. However, scientific evidence is still needed to understand the entire physiological process of dental development, given to their vulnerability to local, systemic, environmental, and genetic factors [19-21]. For more than two decades, it was estimated that over 300 genes are expressed during dental development. Many of these genes actively participate in physiological processes [22]. The expression of TNF-α in tooth germs is described as active in the cytodifferentiation of the odontogenic epithelium [23,24]; IL-1β stimulates gene transcription of the odontogenic protein associated with ameloblast development [25]; Although IL-6 has been widely associated with pulpal inflammation events [26], it has also been described as influential in odontogenic tumors [27], as well as IL-10 [28], suggesting participation in the stages of odontogenesis.

It is essential that evidence of the interaction of estrogen deficiency, genetics factors and dental development be elucidated. The physiological and pathological knowledge of the population may result in preventive and health promotion strategies. Thus, the present study aimed to evaluate the influence of estrogen deficiency on the gene expression of TNF-α, IL-1β, IL-6, and IL-10 during dental development in a murine model.

MATERIAL AND METHODS

Ethical aspects

This research was performed and reported according to the ARRIVE guidelines [29]. The Ethical Committee in Animal Experimentation from the School of Dentistry of Ribeirão Preto, University of São Paulo, Brazil, approved this study (#2018.40.58.3).

Experimental design

Specimens from the study by Madalena et al. [10], sectioned hemimandibles, deficient or not of estrogen, Hypoestrogenism Group (n=8) and Control Group (n=9) respectively, were submitted to the evaluate the gene expression of TNF-α, IL-1β, IL-6 and IL-10 in the odontogenic region using the technique real-time quantitative polymerase chain reaction (RT-qPCR). Conditions of hypofunction (n=4) and dental hyperfunction (n=4) were performed in the animals belonging to the Hypoestrogenism Group as well as, in the Control Group, hypofunction (n=5) and dental hyperfunction (n=4). The experimental design can be observed in Figure 1.

The animals came from the Central Bioterium of the University of São Paulo – Ribeirão Preto Campus. The animals were requested with 21 days of post-uterine life, which corresponds to the pre-pubertal period. Animals that failed in the surgical procedures, that presented dental fractures during the evaluation of the eruption rate and that died before the final evaluation were excluded from the study. Thus, the animals were randomly coded and subsequently proceeded to the randomization of groups and subgroups.

The animals were placed in the Bioterium II at School of Dentistry of Ribeirão Preto, University of São Paulo, in a temperature-controlled environment

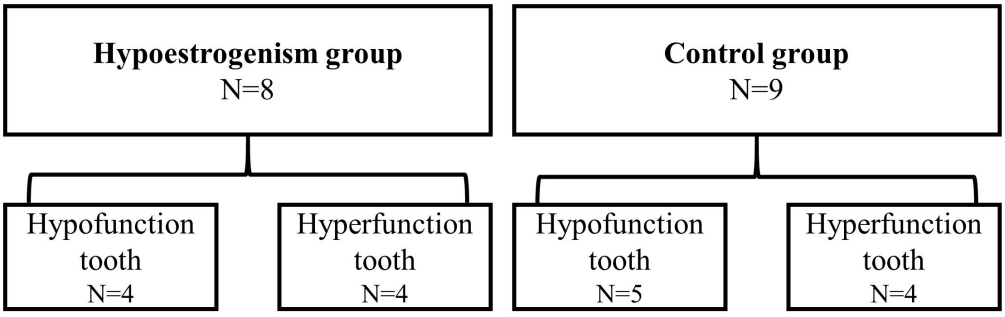

Figure 1 - Experimental design

with a 12-hour light-dark cycle, with free demand for food (Labina Purina®/Agribrands do Brasil LTDA, Paulínia, BR) and filtered water.

Estrogen deficiency model

To create estrogen deficiency a bilateral surgical excision of the ovaries (ovariectomy) was performed in the hypoestrogenism group. While the control group was submitted to fictitious surgery, in which the ovaries were moved and returned to their initial position, as previously described in Omori et al. [6] and Madalena et al. [10]. Surgical procedures were performed under general anesthesia, intramuscularly. The drugs used were 10% Ketamine Hydrochloride (Cetamin® 10%), at a dosage of 55mg/kg and 2% Xylazine Hydrochloride (Xilasyn®), at a dosage of 10mg/kg. After the surgical procedure, antibiotic, anti-inflammatory and analgesic medication was administered. The drugs used were Benzylpenicillin Benzathine (Pentabiotic®) at a dosage of 24,000UI/kg; Flunixine (Aplonal® 1%) at a dosage of 1mg/kg, both intramuscularly, and Tramadol (Cronidor® 2%), at a dosage of 1mg/kg, subcutaneously. Tramadol is also administered again 24 hours after the surgical procedure.

The success of the surgical procedure was confirmed by the animals' survival, gradual increase in body weight during the experimentation period and by the uterine atrophy after euthanasia in the experimental group [6,9,10]. The decrease in endogenous estrogen release, caused by ovariectomy, provides significant differences in the body weight and uterine weight [30].

Dental hypofunction and hyperfunction conditions

To evaluate the odontogenic region, the lower incisors were submitted to conditions of dental hypofunction and hyperfunction. The dental hypofunction condition was performed by incisal adjustment, at the level of the gingival papilla, specifically the mandibular right incisor [9,10,31,32]. Consequently, the homologous mandibular incisor exerted a hyperfunction condition [9,10,31,32]. Mondays, Wednesdays and Fridays were defined, allowing an interval of 48 and 72 hours between incisal edge adjustments. Adjustments were performed for 21 consecutive days (during the entire pubertal period). The incisal adjustment was performed with a 7011 double-sided diamond disc (KG Sorensen®, Cotia, BR) with a thickness of 0.18 mm.

Euthanasia and preparation of specimens

Euthanasia was performed following the guidelines of the National Council for the Control of Animal Experimentation – CONCEA, through anesthetic overdose with Ketamine Hydrochloride (300mg/kg of weight) and Xylazine Hydrochloride (30mg/kg of weight) associated with decapitation. Therefore, the hemimandibles were removed, dissected, and sectioned to isolate the odontogenic region of the dental organ for gene expression analysis as illustrated in previous studies [9,10].

Analysis of TNF-α, IL-1β, IL-6 e IL-10 in odontogenic region – RT-qPCR

The specimens were kept in RNAlater (Life Technologies Corporation - Carlsbad®, Canada, USA) and frozen at -80°C until the day of processing. The mirVana ™ miRNA Isolation kit (Thermo Fischer Scientific, Carlsbad, USA) was used to extract total RNA. Complementary DNA (cDNA) was synthesized by reverse-transcription with a Hight Capacity Kit (Applied Biosystems, Foster City, CA, USA). RT-qPCR was carried out

on a StepOnePlus™ sequence detection system (Applied Biosystems™, Foster City, CA, USA) using TaqMan® primers and probes (Thermo Fisher Scientific, MA, USA) for TNF-α (Rn9999917-m1), IL-1β (Rn00580432-m1), IL-6 (Rn01410330-m1) e IL-10 (Rn00563409-m1). GAPDH (Rn01462661-g1) and ACTB (Rn01412977-g1) were used as endogenous controls. The relative levels of mRNA expression were determined by the $2^{-\Delta\Delta}$ Cycle Threshold ($2^{-\Delta\Delta CT}$) method [16]. Both, GAPDH and ACTB, genes were used for sample normalization to calculate the relative quantification. The mean of both genes was used. All procedures were performed following the respective manufacturer's instructions and according to established protocols.

Statistical analysis

The data were evaluated using the GraphPad Prism 7.04 software (GraphPad Software®, La Jolla, USA). The gene expression of the TNF-α, IL-1β, IL-6 e IL-10 were expressed as mean ± standard deviation (SD). Kruskal-Wallis test and Dunn's posttest were performed. The level of significance was 5%. A post hoc power estimation was performed in Clincalc.com®.

RESULTS

Body weight gain was higher in the group submitted to hypoestrogenism when compared to the control group ($p=0.002$). Uterine atrophy was also noted in the group submitted to hypoestrogenism when compared to the control group ($p\leq 0.0001$).

Table I shows the comparison between the hypoestrogenism and control groups under the conditions of dental hypofunction and hyperfunction. There were statistically significant differences of TNF-α and IL-1β gene expression between the hypoestrogenism and control groups under condition of dental hypofunction ($p=0.0084$, $p=0.0072$, respectively). Power calculations indicated that we had a power ranging from 6% to 99%.

DISCUSSION

Gaps in genes involved in dental development still exist. In parallel, it is important to mention that the expression of ERβ described in cells that participate in dental development implies research that complements the action of estrogen and its related genes. Thus, the present study aimed to evaluate the influence of estrogen deficiency on the gene expression of TNF-α, IL-1β, IL-6, and IL-10 during dental development in a murine model. Our results demonstrate that in estrogen deficiency and dental hypofunction conditions, there is a significant increase in TNF-α while a significant decrease in IL-1β is also noted.

Studies in murine models are classic when the objective is to elucidate local, systemic, environmental, and genetic influences on

Table I - Gene expression of TNF-α, IL-1β, IL-6 and IL-10 in the odontogenic region in dental organ of the lower incisors of both groups, in teeth with occlusal hypofunction and hyperfunction

Groups	Hypoestrogenism		Control		*p-value*
	Hypofunction tooth	Hyperfunction tooth	Hypofunction tooth	Hyperfunction tooth	
			TNF-α		
Mean (SD)	2.87 (0.87)	1.97 (0.81)	0.90 (0.23)	1.22 (0.36)	*0.0072**
Min.-Max.	2.14 – 4.14	1.42 – 3.18	0.55 – 1.22	0.74 – 1.52	
			IL-1β		
Mean (SD)	0.72 (0.45)	0.35 (0.15)	1.27 (0.33)	0.80 (0.28)	*0.0084**
Min.-Max.	0.39 – 1.38	0.14 - 0.51	0.86 – 1.77	0.51 – 1.16	
			IL-6		
Mean (SD)	1.82 (0.67)	0.88 (0.27)	0.93 (0.20)	1.28 (0.82)	*0.092*
Min.-Max.	1.17 – 2.45	0.56 – 1.22	0.69 – 1.14	0.62 – 2.41	
			IL-10		
Mean (SD)	2.01 (1.17)	0.63 (0.26)	0.83 (0.39)	1.78 (1.18)	*0.104*
Min.-Max.	0.78 – 3.44	0.37 – 0.99	0.38 – 1.31	0.45 – 2.81	

*Statistically significant difference.

the development and process of tooth eruption [9,10,31-33]. It is noteworthy that the murine model has continuous development and eruption of incisors, which results in a broad regenerative capacity of the odontogenic region. Furthermore, it is suggested that there is an important applicability of these studies with human samples due to the similarity of dental development stages [9,10,31-33]. Several authors have also reported that shortening or adjustment of the incisal edge of the incisor (hypofunctional condition) can lead to a marked increase in eruption rate and clearly replicate changes associated with tooth eruption rate [31,34,35]. It is hypothesized that tooth development may also change under conditions of hypofunctionality and hyperfunctionality.

Estrogen is a steroid hormone that has been extensively studied today [4-10]. In addition to its physiological importance to many vital tissues and organs and the pubertal development of girls and boys [2], estrogenic effects have been attributed to harmful effects from exposure to synthetic compounds widely distributed in the environment. Recent scientific evidence points to the presence of the main estrogen receptors, ERα and ERβ, encoded by the *ESR1* and *ESR2* genes, respectively, in the dental organ of teeth in continuous growth in the estrogen-deficient murine model, influencing patterns of development by the supposed action in mesenchymal cells [8,9].

Some inflammatory cytokines, especially TNF-α, are increased when estrogen is deficient. It is estimated that TNF-α can inhibit the osteogenic differentiation of mesenchymal stem cells [12]. Our results corroborate the increase in TNF-α expression in estrogen deficiency. Furthermore, it is possible to suggest that an inflammatory process occurs with the potential to disrupt odontogenesis and, consequently, the rate of tooth eruption, as described by Madalena et al. [10]. In contrast, the increase in TNF-α expression was not sufficient to induce IL-6 expression in the continuously growing tooth organ. It is therefore suggested that the overexpression of ERβ in the odontogenic region of incisors of animals subjected to estrogen deficiency [10] has acted as a protective factor and contributed to the reduction of IL-6 and IL-1β expression levels in lipopolysaccharide (LPS)-induced PC-3 cells [36]. LPS is a common inducer of inflammation; exposure leads to the activation of several components involved in chronic inflammation processes, such as altered levels of cytokines [36]. It is suggested the need to complement the results by showing other cytokines that could be involved in the process of odontogenesis and even tooth eruption.

It is true to say that the vast majority of studies and scientific evidence involving gene expression in teeth during development are limited to animal models, especially in the murine model [6,8-10,37,38]. The murine model allows an interesting reproducibility of human development because more than 90% of its genome can be divided into regions corresponding to that of humans. However, such premises do not exclude the need for further studies related to the expression of cytokines and TNF-α in human tooth development.

In summary, this study showed that estrogen deficiency interfered with the gene expression of the interleukins TNF-α and IL-1β. The lack of estrogen affect the expression of TNF-α. It is suggested that odontogenesis undergoes a delay in its process; moreover, the lack of estrogen negatively affected the expression of IL-1β, suggesting that the overexpression of estrogen receptors ERβ acted as a potentially protective factor against the inflammatory process.

CONCLUSION

Estrogen deficiency influences TNF-α and IL-1β gene expression in the odontogenic region in dental hypofunctional condition.

Acknowledgements

We also thank to São Paulo Research Foundation - FAPESP and the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – CAPES/Brasil.

Author's Contributions

IDA: Writing-original draft preparation. VON: Writing-original draft preparation. MFRT: Writing-original draft preparation. LAR: Methodology and investigation. PNF: Conceptualization. ECK: Conceptualization and funding acquisition. MAHMO: Writing – review and editing. CPL: Writing—review and editing. FBF: Writing – review and editing. IRM:

Methodology and investigation and funding acquisition.

Conflict of Interest

The authors declare that they have no conflict of interest.

Funding

This research was funded by the São Paulo Research Foundation - FAPESP (process #2015/06866-5 and #2016/08149-1) and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES-Brasil) – PDPG-POSDOC/Bolsa - CAPES nº 88887.755620/2022-00.

Regulatory Statement

This study was conducted in accordance with all the provisions of the local human subjects oversight committee guidelines and policies of: The Ethical Committee in Animal Experimentation from the School of Dentistry of Ribeirão Preto, University of São Paulo, Brazil. The approval code for this study is: 2018.40.58.3.

REFERENCES

1. Patel S, Homaei A, Raju AB, Meher BR. Estrogen: the necessary evil for human health, and ways to tame it. Biomed Pharmacother. 2018;102:403-11. http://dx.doi.org/10.1016/j.biopha.2018.03.078. PMid:29573619.
2. Almeida M, Laurent MR, Dubois V, Claessens F, O'Brien CA, Bouillon R, et al. Estrogens and androgens in skeletal physiology and pathophysiology. Physiol Rev. 2017;97(1):135-87. http://dx.doi.org/10.1152/physrev.00033.2015. PMid:27807202.
3. Christ JP, Gunning MN, Palla G, Eijkemans MJC, Lambalk CB, Laven JSE, et al. Estrogen deprivation and cardiovascular disease risk in primary ovarian insufficiency. Fertil Steril. 2018;109(4):594-600. http://dx.doi.org/10.1016/j.fertnstert.2017.11.035. PMid:29605405.
4. Küchler EC, Gerlach RF, Cunha AS, Ramazzotto LA, Spada PP, Nelson-Filho P, et al. Calcium and phosphorus levels in saliva are influenced by genetic polymorphisms in estrogen receptor alpha and microrna17. Braz Dent J. 2020;31(5):466-70. http://dx.doi.org/10.1590/0103-6440202002934. PMid:33146328.
5. Küchler EC, Meger MN, Omori MA, Gerber JT, Martins EC No, Machado NCS, et al. Association between oestrogen receptors and female temporomandibular disorders. Acta Odontol Scand. 2020;78(3):181-8. http://dx.doi.org/10.1080/00016357.2019.1675904. PMid:31646926.
6. Omori MA, Marañón-Vásquez GA, Romualdo PC, Martins EC No, Stuani MBS, Matsumoto MN, et al. Effect of ovariectomy on maxilla and mandible dimensions of female rats. Orthod Craniofac Res. 2020a;23(3):342-50. http://dx.doi.org/10.1111/ocr.12376. PMid:32246880.
7. Omori MA, Gerber JT, Marañón-Vásquez GA, Matsumoto MAN, Weiss SG, Nascimento MA, et al. Possible association between craniofacial dimensions and genetic markers in *ESR1* and *ESR2*. J Orthod. 2020b;47(1):65-71. http://dx.doi.org/10.1177/1465312520901725. PMid:32000574.
8. Küchler EC, de Lara RM, Omori MA, Schröder A, Teodoro VB, Baratto-Filho F, et al. Estrogen deficiency affects tooth formation and gene expression in the odontogenic region of female rats. Ann Anat. 2021;236:151702. http://dx.doi.org/10.1016/j.aanat.2021.151702. PMid:33607226.
9. Madalena IR, Judachesci CS, Küchler EC, Nelson-Filho P, Ramazzotto LA, Baratto-Filho F, et al. The impact of hypoestrogenism and occlusal function on MMP1, MMP8 and MMP13 expression in the odontogenic region in rats. RSDJournal. 2021;10(5):e47810515311. http://dx.doi.org/10.33448/rsd-v10i5.15311.
10. Madalena IR, Marañón-Vásquez GA, Omori MA, de Sousa ET, da Silveira HA, León JE, et al. Evaluation of tooth eruption rate of incisor teeth in rats with estrogen deficiency. Clin Oral Investig. 2022;27(1):345-52. http://dx.doi.org/10.1007/s00784-022-04738-w. PMid:36260168.
11. Ahmed SF, Achermann JC, Arlt W, Balen A, Conway G, Edwards Z, et al. Society for Endocrinology UK guidance on the initial evaluation of an infant or an adolescent with a suspected disorder of sex development (Revised 2015). Clin Endocrinol (Oxf). 2016;84(5):771-88. http://dx.doi.org/10.1111/cen.12857. PMid:26270788.
12. Yang N, Wang G, Hu C, Shi Y, Liao L, Shi S, et al. Tumor necrosis factor α suppresses the mesenchymal stem cell osteogenesis promoter miR-21 in estrogen deficiency-induced osteoporosis. J Bone Miner Res. 2013;28(3):559-73. http://dx.doi.org/10.1002/jbmr.1798. PMid:23074166.
13. Confalone E, D'Alessio G, Furia A. IL-6 Induction by TNFα and IL-1β in an osteoblast-like cell line. Int J Biomed Sci. 2010;6(2):135-40. PMid:23675187.
14. Ruscitti P, Cipriani P, Carubbi F, Liakouli V, Zazzeroni F, Di Benedetto P, et al. The role of IL-1β in the bone loss during rheumatic diseases. Mediators Inflamm. 2015;2015:782382. http://dx.doi.org/10.1155/2015/782382. PMid:25954061.
15. Luo Y, Zheng SG. Hall of fame among pro-inflammatory cytokines: interleukin-6 gene and its transcriptional regulation mechanisms. Front Immunol. 2016;7:604. http://dx.doi.org/10.3389/fimmu.2016.00604. PMid:28066415.
16. Wang Y, Zhang W, Lim SM, Xu L, Jin JO. Interleukin-10-producing B cells help suppress ovariectomy-mediated osteoporosis. Immune Netw. 2020;20(6):e50. http://dx.doi.org/10.4110/in.2020.20.e50. PMid:33425435.
17. Vucic S, Dhamo B, Jaddoe VWV, Wolvius EB, Ongkosuwito EM. Dental development and craniofacial morphology in school-age children. Am J Orthod Dentofacial Orthop. 2019;156(2):229-237.e4. http://dx.doi.org/10.1016/j.ajodo.2018.09.014. PMid:31375233.
18. Manlove AE, Romeo G, Venugopalan SR. Craniofacial growth: current theories and influence on management. Oral Maxillofac Surg Clin North Am. 2020;32(2):167-75. http://dx.doi.org/10.1016/j.coms.2020.01.007. PMid:32151371.
19. Atar M, Körperich EJ. Systemic disorders and their influence on the development of dental hard tissues: a literature review. J Dent. 2010;38(4):296-306. http://dx.doi.org/10.1016/j.jdent.2009.12.001. PMid:20004698.
20. Li C, Cui Y, Zhou C, Sun J, Zhou X. Epigenetics in odontogenesis and its influences. Curr Stem Cell Res Ther. 2018;13(2):110-7. http://dx.doi.org/10.2174/1574888X12666170530100524. PMid:28554314.
21. Youssef AR, Emara R, Taher MT, Al-Allaf FA, Almalki M, Almasri MA, et al. Effects of mineral trioxide aggregate, calcium hydroxide, biodentine and Emdogain on osteogenesis,

odontogenesis, angiogenesis and cell viability of dental pulp stem cells. BMC Oral Health. 2019;19(1):133. http://dx.doi.org/10.1186/s12903-019-0827-0. PMid:31266498.

22. Galluccio G, Castellano M, La Monaca CL. Genetic basis of non-syndromic anomalies of human tooth number. Arch Oral Biol. 2012;57(7):918-30. http://dx.doi.org/10.1016/j.archoralbio.2012.01.005. PMid:22325622.

23. Kumamoto H, Ooya K. Expression of tumor necrosis factor alpha, TNF-related apoptosis-inducing ligand, and their associated molecules in ameloblastomas. J Oral Pathol Med. 2005;34(5):287-94. http://dx.doi.org/10.1111/j.1600-0714.2005.00311.x. PMid:15817072.

24. Tsuruya Y, Yamaguchi A, Yamazaki-Takai M, Mezawa M, Takai H, Nakayama Y, et al. Transcriptional regulation of human odontogenic ameloblast-associated protein gene by tumor necrosis factor-α. Inflamm Res. 2022;71(1):119-29. http://dx.doi.org/10.1007/s00011-021-01523-5. PMid:34787682.

25. Tsuruya Y, Yamaguchi A, Yamazaki-Takai M, Zhenyu J, Takai H, Nakayama Y, et al. Interleukin-1β regulates odontogenic ameloblast-associated protein gene transcription in human gingival epithelial cells. Odontology. 2022;110(3):557-68. http://dx.doi.org/10.1007/s10266-022-00689-6. PMid:35179670.

26. Fujii M, Kawashima N, Tazawa K, Hashimoto K, Nara K, Noda S, et al. HIF1α inhibits LPS-mediated induction of IL-6 synthesis via SOCS3-dependent CEBPβ suppression in human dental pulp cells. Biochem Biophys Res Commun. 2020;522(2):308-14. http://dx.doi.org/10.1016/j.bbrc.2019.11.032. PMid:31767145.

27. Sengüven B, Oygür T. Investigation of interleukin-1 alpha and interleukin-6 expression and interleukin-1 alpha gene polymorphism in keratocystic odontogenic tumors and ameloblastomas. Med Oral Patol Oral Cir Bucal. 2011;16(4):e467-72. http://dx.doi.org/10.4317/medoral.16.e467. PMid:21196890.

28. Sá MC, de Matos FR, Conceição TS, Leitão ACGH, Freitas RA. Immunoexpression of tumour necrosis factor-α, interleukin-1α and interleukin-10 on odontogenic cysts and tumours. Int Endod J. 2017;50(5):437-45. http://dx.doi.org/10.1111/iej.12640. PMid:27009845.

29. Kilkenny C, Browne WJ, Cuthill IC, Emerson M, Altman DG. Improving bioscience research reporting: the ARRIVE guidelines for reporting animal research. PLoS Biol. 2010;8(6):e1000412. http://dx.doi.org/10.1371/journal.pbio.1000412. PMid:20613859.

30. Chen X, Cai C, Liu J, Wen L, Wang X, Ding Y. Impact of estrogen-related receptor α on the biological characteristics of rat mandibular condylar chondrocytes. Mol Med Rep. 2014;10(1):195-202. http://dx.doi.org/10.3892/mmr.2014.2210. PMid:24805131.

31. Gomes JR, Omar NF, Do Carmo ER, Neves JS, Soares MAM, Narvaes EA, et al. Relationship between cell proliferation and eruption rate in the rat incisor. Anat Rec (Hoboken). 2013;296(7):1096-101. http://dx.doi.org/10.1002/ar.22712. PMid:23629828.

32. Silva MAD, Vasconcelos DFP, Marques MR, Barros SP. Parathyroid hormone intermittent administration promotes delay on rat incisor eruption. Arch Oral Biol. 2016;69:102-8. http://dx.doi.org/10.1016/j.archoralbio.2016.05.017. PMid:27285944.

33. Omar NF, Gomes JR, Neves JS, Novaes PD. Effects of loss of occlusal contact on the expression of matrix metalloproteinase-2, membrane type 1-MMP, tissue inhibitor of the MMP-2, eruption rate, organization and resistance of collagen fibers of the rat incisor periodontal ligament. J Periodontal Res. 2018;53(1):40-6. http://dx.doi.org/10.1111/jre.12484. PMid:29044524.

34. Gerlach RF, Toledo DB, Novaes PD, Merzel J, Line SRP. The effect of lead on the eruption rates of incisor teeth in rats. Arch Oral Biol. 2000;45(11):951-5. http://dx.doi.org/10.1016/S0003-9969(00)00072-8. PMid:11000381.

35. Lee CK, Law KT, King NM, Rabie ABM. A comparison between a conventional optical method and image-analysis for measuring the unimpeded eruption rate of the rat mandibular incisor. Arch Oral Biol. 2002;47(7):555-62. http://dx.doi.org/10.1016/S0003-9969(02)00039-0. PMid:12208080.

36. Xiao L, Luo Y, Tai R, Zhang N. Estrogen receptor β suppresses inflammation and the progression of prostate cancer. Mol Med Rep. 2019;19(5):3555-63. http://dx.doi.org/10.3892/mmr.2019.10014. PMid:30864712.

37. Järvinen E, Shimomura-Kuroki J, Balic A, Jussila M, Thesleff I. Mesenchymal Wnt/β-catenin signaling limits tooth number. Development. 2018;145(4):dev158048. http://dx.doi.org/10.1242/dev.158048. PMid:29437780.

38. Rostampour N, Appelt CM, Abid A, Boughner JC. Expression of new genes in vertebrate tooth development and p63 signaling. Dev Dyn. 2019;248(8):744-55. http://dx.doi.org/10.1002/dvdy.26. PMid:30875130.

Isabela Ribeiro Madalena
(Corresponding address)
Centro Universitário Presidente Tancredo de Almeida Neves, Faculdade de Odontologia. São João del Rei, MG, Brazil.
Email: isabelarmadalena@hotmail.com

Date submitted: 2022 Jan 26
Accept submission: 2023 Mar 04