Scientific Knowledge Group

Letter to Editor

Journal of Dental and Maxillofacial Medicine

Odontogenesis and Tumorigenesis

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Abstract
Odontogenesis is the complex process by which teeth form from embryonic cells, grow, and erupt into the mouth. The primitive oral cavity, or stomodeum, is lined by stratified squamous epithelium called the oral ectoderm or primitive oral epithelium.

Keywords: Odontogenesis, Tooth Development, Tooth Agenesis, Hypodontia, Oligodontia.

Received: December 17, 2025;
Accepted: December 24, 2025;
Published: January 02, 2026

Odontogenesis is the complex process by which teeth form from embryonic cells, grow, and erupt into the mouth. The primitive oral cavity, or stomodeum, is lined by stratified squamous epithelium called the oral ectoderm or primitive oral epithelium [1]. The oral ectoderm contacts the endoderm of the foregut to form the buccopharyngeal membrane [1,2]. At about the 27 days of gestation this membrane ruptures and the primitive oral cavity establishes a connection with the foregut. Most of the connective tissue cells underlying the oral ectoderm are of neural crest or ectomesenchyme in origin. These cells are thought to anterior portion of what will be instructor induce the overlying ectoderm to start tooth development, which begins in the future maxilla and mandible and proceeds posteriorly. Teeth development results from an interaction of the oral epithelial cells and the underlying ectomesenchyme cells. From this interaction, 20 deciduous and 32 permanent teeth developed. Each developing tooth grows as an anatomically distinct unit. The fundamental developmental process is similar for all teeth (deciduous & permanent teeth) [1-5].

Dental organ or tooth germ: is a term used to constitute the structure that has enamel organ, dental papilla and dental follicle. Primary epithelial band: Two or three weeks after the rupture of the buccopharyngeal membrane, when the embryo is about 6 weeks old, certain areas of basal cells of the oral ectoderm proliferate more rapidly than do the cells of the adjacent areas [1-6]. This leads to the formation of the Primary epithelial band which is a band of epithelium that has invaded the underlying ectomesenchyme along each of the horseshoe-shaped future dental arches. At about 7th week the primary epithelial band divides into an inner (lingual) process called Dental lamina and an outer (buccal) process called Vestibular lamina [1-7].

Rapid increase of knowledge in stem cell research, bioengineering technology and molecular basis of odontogenesis has finally led us to the point where it is possible to develop approaches for treatment of tooth loss with bioengineered teeth, which one day might supplement and replace conventional prosthodontics and dental implants [1-4]. What puts tooth bioengineering in the forefront of bio-regenerative medicine are the very features of tooth as an organ. Teeth are easily accessible, non-essential for life organs of relatively simple structure with their own complement of various stem cells niches There are at least three possible ways to bioengineer tooth - to build and then to

Citation: Abu-Hussein Muhamad (2026) Odontogenesis and Tumorigenesis. J Dent Maxillofac Med 1: 1-4.

assemble individual tooth components crown, root; putting aggregates of dental stem cells to spontaneously re-organize within tooth-shape customized scaffolds; and to transplant artificially created tooth germs into adult jaws until they develop into functional teeth [1-8].

There are two major theories about variability of tooth shapes in different mammalian species. According to one theory, this occurs due to introduction of new genetic networks, whereas the other one suggests that variability of tooth shapes is not the consequence of introduction of new genetic networks, but rather the outcome of modulating the existing ones. Continuously growing rodent incisors are perfect model for investigating the mechanisms which regulate maintenance and function of stem cell niches [1-3]. Namely, roots of those teeth harbor permanently active cervical loops driven by non-depleting complement of stem cells. Rodent incisor stem cell niche resides within the stellate reticulum, a vacuolated tissue compartment enclosed by a single layer basal epithelium of cervical loops. Mesenchymal cells surround the epithelium and provide regulatory signals, which determine proliferation and self-renewal or differentiation of stem cells. Balance is established by co expression of various growth factors FGF-3, FGF-10, BMP-4, their inhibitors Activin, Sprouty genes, Noggin and by all-round inhibitors Folli statin which seem to be capable to inhibit both growth factor and its immediate inhibitor [1-3,6-11].

This type of functional redundancy is quite an astonishing display of regulatory network plasticity and subsequent phenotype is no less strange - cervical loops of rodent incisors are asymmetric labial one being wider than the lingual one, which is reflected by exclusive deposition of enamel on the labial side. Interestingly, knocking out any of those inhibitors or simultaneously a group of inhibitors always leads to substantial enlargement of crown [11-14]. However, in some cases crown ends up with enamel being deposited on both labial and lingual side, while in other cases there is no enamel at all. These examples show how striking lapses between dental phenotypes non-continuously growing teeth vs. continuously growing teeth can be caused by slight modulation of existing genetic regulatory networks [10]. Any kind of altering of activity or resilience of stem cell niches in cervical loops dramatically affects the basic outlook of a tooth. Namely, continuously growing teeth have extremely tall crowns in contrast to relatively short roots hypodontia. They also point out to a possible operational mode in genetic regulatory networks for setting up the timing of transition from development of crown to development of root [1-10]. So far, that particular time-frame of odontogenesis has been relatively poorly investigated.

Research in cell biology and human genetics has shown genetic overlap in the occurrence of tooth agenesis and certain human cancers[11-15]. Although the process of odontogenesis may seem unrelated to tumorigenesis, various case series have reported an association between tooth agenesis and tumors in humans [13,15,16].

In 2004, Lammi et al reported on 4 generations of a Finnish family (12 family members) and described the association between familial tooth agenesis (oligodontia) and colorectal neoplasms [12]. Mutations in the AXIN2 gene identified in this familial group were inherited in an autosomal dominant pattern. Colorectal neoplasia (ranging from polyps to colorectal cancer) was found in 6 family members with oligodontia. Neoplasia was not identified in family members with a normal complement of teeth. Through DNA isolation from venous blood and molecular analysis, nonsense and frameshift mutations in the AXIN2 gene were identified. In addition to its role in odontogenesis, the AXIN2 gene regulates the went pathway and thereby controls cellular proliferation, differentiation, and morphogenesis of organ systems [12]. The Lammi et al. familial analysis provided evidence of the genetic overlap between colorectal neoplasia and oligodontia linked to AXIN2 mutations [17]. In addition to this study, AXIN2 mutations have been identified in several human cancers, including colorectal, skin, gastrointestinal, liver, and ovarian cancer [1-13]. In 2011, Marvin et al. evaluated 3 generations of a family with autosomal dominant oligodontia [14]. They detected a nonsense mutation on the AXIN2 gene leading to the phenotype of oligodontia. The family members with the gene mutation and oligodontia also exhibited neoplasms: early onset breast cancer, colorectal cancer, and gastrointestinal adenomas. Family members without oligodontia did not present with neoplasms [14]. In 2008, Chalo thorn et al. reported hypodontia as a marker for epithelial ovarian cancer. In their comparison of 50 females with epithelial ovarian cancer and 100 healthy females without epithelial ovarian cancer, 20% of patients with epithelial ovarian cancer had hypodontia compared to 3% of healthy controls, and the difference was statistically significant ($P < 0.001$). Patients with epithelial ovarian cancer were 8.1 times more likely to have hypodontia than the healthy controls [15]. In 2015, Fekonja et al also investigated the occurrence of epithelial ovarian cancer in females with hypodontia. In this retrospective study, 150 Slovenian females with epithelial ovarian cancer were compared to age-matched healthy women. The incidence of hypodontia was 19.2% of females with epithelial ovarian cancer vs 6.7% in healthy controls. The difference was statistically significant ($P = 0.004$) with an odds ratio of 3.32. Further, poorly differentiated tumors were observed in a significantly higher proportion of patients with hypodontia than in patients without hypodontia ($P = 0.042$). Patients with hypodontia also had a significantly higher incidence of bilateral epithelial ovarian cancer ($P = 0.02$).

The correlation between epithelial ovarian cancer and hypodontia is particularly important as epithelial ovarian cancer is considered a fatal malignancy and a silent killer in women. Ovarian cancer is difficult to diagnose because of the lack of effective screening markers. The most effective screening risk factor is a familial history of epithelial ovarian cancer. Tooth agenesis could potentially serve as a noninvasive screening tool to identify patients at risk early in life [17]. In 2013, Küchler et al conducted a cross-sectional single-center study in Brazil, 4 recruiting 82 patients with tooth agenesis and 328 age-matched controls for the study. Familial history of cancer was collected from all study participants. Patients with tooth agenesis had a significantly higher risk of having a family history of cancer ($P = 0.00006$, odds ratio 2.7) than the control group [16]. Breast cancer was the most commonly reported cancer, followed by prostate cancer and cancers of the brain and nervous system. Individuals with tooth agenesis also had a higher risk of having

a family history of female cancers (breast, ovarian, and cervical uterine cancer). The results highlight the potential association between tooth agenesis and neoplasms [16].

The genetic etiology of tooth agenesis is an area of academic endeavor that has grown between 2003-2018 because of advances in the understanding of genetic and molecular interactions. Genetic mutations in key genes regulating odontogenesis lead to failure of tooth development. The same mutations may be associated with the development of neoplasms that are detected later in life [1-9]. The link between tumorigenesis and odontogenesis suggests the plausibility of using hypodontia in childhood as a screening tool or marker for the risk of neoplasms in adulthood. The dentist can detect tooth agenesis within the first decade of life and is therefore in a unique position to counsel the child's family and physician of the dental findings with respect to potential risks of neoplasms later in life. Similarly, when pediatricians notice unusual spacing between teeth during well-check visits or elicit a family history of missing teeth, they should ensure that a complete dental assessment for tooth agenesis is performed [1,12].

Tooth agenesis has a psychosocial impact, functional limitations, and ongoing dental treatment–related expenses that present challenges to patients and their families. [1-12] Consequently, dental professionals focus on the management of function and esthetics throughout the growing years of a child with tooth agenesis, and successful dental management usually requires interdisciplinary care involving a pediatric dentist, orthodontist, and prosthodontist [1-11]. However, in light of the research showing the link between tooth agenesis and cancer, the pediatric dentist should also include a discussion of risk for adult neoplasms in the anticipatory guidance provided to children with hypodontia and their caregivers and forward a summary of dental findings to the child's primary medical care providers [15-20].

The emerging understanding between tooth agenesis and the development of neoplasms in adulthood is based on studies in molecular biology and the genetics of odontogenesis and on clinical reports. These studies have limitations, including sample sizes, ethnicity of study subjects, and incompletely identified genetic markers or molecular processes. Prospective clinical and genetic studies are needed to determine if hypodontia is an unequivocal marker for adult neoplasms [19,20].

The literature shows a link between tooth agenesis and neoplastic changes that may be one of association rather than of cause and effect. However, this potential association identifies the importance of the oral-systemic health continuum and underscores the importance of collaborative care among all healthcare providers, including dentists and physicians.

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