OXFORD JOURNAL
OF STUDENT
SCHOLARSHIP

USAG-1 Inhibition for Tooth Regeneration: Therapeutic Potential and Possible Risks - A Literature Review

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ABSTRACT

Teeth are important organs for humans with multiple functions, including chewing food and speaking clearly. Losing their teeth can affect their quality of life. People not only may lose their teeth through acquired causes but also congenitally due to genetic causes. USAG-1 is targeted for the study of tooth regeneration. This paper examines the inhibition of USAG-1 for tooth regeneration and the potential risks for its therapeutic use. USAG-1 acts as an antagonist for the Wnt and BMP signaling pathways, which are critical for the development of teeth. By inhibiting USAG-1, research suggests that it can rescue arrested and rudimentary tooth germs in animal studies. Anti-USAG-1 neutralizing antibodies therapy shows potential for tooth regeneration. However, USAG-1 is also expressed in other nondental tissues. Research shows that USAG-1 has been associated with the progression of cancer cells. The inhibition of USAG-1 for tooth regeneration may affect other parts of the body. Therefore, long-term research for the effects of inhibition of USAG-1 is needed before the therapeutic use for tooth regeneration in humans.

INTRODUCTION

Tooth loss is a major problem that affects people of all ages. Tooth loss can adversely affect their health and quality of life. Currently, the most common tooth replacement options for tooth loss are dental implants, dentures, and bridges. Even though these methods are highly effective, they are artificial and have limitations according to the patient's age and jawbone development. As a result, scientists are considering the possibility of biological regeneration of teeth. One of their approaches is to target their research on the USAG-1 gene. The study of USAG-1 using animal models suggests that inhibiting USAG-1 may promote tooth regeneration. However, the differences in tooth development between animal models and humans may limit the effectiveness of the treatments. Also, studies of some cancers found a reduction in USAG-1 expression, suggesting a potential role of suppressing tumors. These findings raise concerns about potential cancer-related risks. However, there is a lack of direct evidence demonstrating that inhibition of USAG-1 may cause cancer. As a result, more testing is required to evaluate the effects on non-dental tissues, such as potential effects on cancer development, and long-term safety before the actual application on humans.

BACKGROUND OF TOOTH DEVELOPMENT

Stages of Tooth Development

Odontogenesis, tooth development, is a complex process that involves the interaction called epithelium-ectomesenchyme interaction between two different types of tissue: oral epithelium and ectomesenchyme. Oral epithelium is the outer layer of cells in the embryo's mouth. Ectomesenchyme, comes from cranial neural crest cells, is the tissue underneath the epithelium. Teeth develop by continuous communications between the two tissues, oral epithelium and ectomesenchyme, through signaling pathways, such as Wnt, BMP, and Shh. About 6 to 8 weeks of pregnancy, the oral epithelium becomes thicker and extends down into ectomesenchyme. This forms a structure known as the dental lamina. This marks the first visible sign of tooth formation. Tooth germ is composed of three main parts: enamel organ, dental papilla, and dental follicle. Each of them has different future roles in tooth development. Enamel organ, originating from oral epithelium, will form enamel. Dental papilla, originating from ectomesenchyme, will make dentin and pulp. Dental follicles, originating also from ectomesenchyme, will form supporting tissues, such as cementum, periodontal ligament, and alveolar bone (Novacescu et al., 2025).

First, it's the bud stage, where dental lamina develops downward into ectomesenchyme and forms a little round bump called the tooth bud. In this stage, cells divide rapidly and the future location of every tooth is determined. However, cells are not specialized at this stage. Dental papilla and dental follicle start forming (Novacescu et al., 2025).

The second stage is the cap stage, where the tooth bud grows larger and bends inward into a cap shape. At this stage, the three main parts become more visible. The enamel organ looks like a cap, dental papilla forms inside the cap, and dental follicles surround both enamel organ and dental papilla (Novacescu et al., 2025).

The third stage is the bell stage, where the enamel organ becomes bell shaped. In this stage, cells become specialized, which is called cell differentiation. In the early stage, tooth shapes are finalized, layers become organized, dental papilla forms odontoblasts, which are specialized cells that produce dentin. The inner epithelium of the enamel organ forms ameloblasts, which are specialized cells that produce enamel. Cells begin to prepare for secretion. In the late stage, cell secretion begins. Odontoblasts secrete predentin. Predentin then mineralizes into dentin. After dentin exists, ameloblasts begin secreting the enamel matrix and mineralizes into hard and mature enamel (Novacescu et al., 2025).

The fourth stage is the apposition stage. In this stage, odontoblasts continue to produce dentin, and ameloblasts continue to produce enamel. Both tissues grow layer by layer, gradually building the hard structure of the tooth. Once the enamel deposition is finished, the enamel organ collapses and becomes the reduced enamel epithelium (REE). This layer covers and protects the enamel until the tooth erupts (Novacescu et al., 2025).

Next, it's the root formation, which happens after the crown is complete. The cervical loop of the enamel

organ grows downward to form a new structure called Hertwig's epithelial root sheath (HERS), which acts as a mold for the shape of the root. HERS triggers the differentiation of dental papilla cells into odontoblasts for producing root dentin. After the formation of root dentin, HERS disintegrates. Then, the cells from the dental follicle come into contact with the roots and form cementoblasts, fibroblasts, and osteoblasts. Cementoblasts produce cementum, covering the tooth root. Fibroblasts produce periodontal ligament, connecting tooth root to jawbone. Osteoblasts produce alveolar bone, holding the tooth. As the tooth root grows longer, teeth begin to erupt. The reduced enamel epithelium merges with the oral epithelium, creating an eruption pathway. Teeth gradually emerge into the oral cavity (Novacescu et al., 2025).

Wnt and BMP Signaling Pathways

Bone morphogenetic protein (BMP) signaling pathways regulate dental stem cell differentiation and proliferation. It begins when BMP proteins bind to the BMP receptors. Through binding, it activates signals that can direct dental stem cells to develop into specialized cells, such as odontoblasts, which form dentin. If BMP signaling is disrupted, it can result in early arrested tooth development, affecting the normal formation of teeth (Zhang et al., 2016). In addition, Wnt signaling pathways contribute to tooth development. When Wnt proteins bind to the receptors, β-catenin accumulates and helps regulate genes involved in cell differentiation, proliferation, and apoptosis. Furthermore, the Wnt signaling pathway helps in the regulation of the tooth numbers. As a result, it should also be properly controlled during the development of teeth. Both of the signaling pathways are essential in the development of teeth. They interact with each other antagonistically and synergistically depending on different dental cells. Their crosstalk guides and coordinates the normal formation of teeth. During the development of teeth, USAG-1 protein binds to the LRP4 receptor to coordinate the Wnt and BMP signaling pathways for proper formation of teeth (Zhang et al., 2016).

The Role of USAG-1 Gene in Tooth Development

USAG-1 is a gene that stands for Uterine Sensitization-Associated Gene. It is also identified as SOSTDC-1 and Wise. It encodes the USAG-1 protein, which is a secreted protein that can determine how cells develop. It plays an important role as an antagonist of the Wnt and BMP signaling pathways, which are important signaling pathways that control tooth development. In the BMP signaling pathway, USAG-1 acts as an antagonist of BMP-7 protein, which reduces the signal of BMP pathway. This can cause the rudimentary tooth germ to stop developing (Tong et al., 2022). In addition, USAG-1 limits the activity of Wnt proteins, such as Wnt1and Wnt3a. This blocks the Wnt signaling pathways, which can direct tooth number and shape. Previous research suggested that mice lacking the USAG-1 gene may develop abnormal tooth shape and extra teeth (Tong et al., 2022). As a result, USAG-1 is crucial in tooth development and the study of tooth regeneration.

HOW INHIBITING USAG-1 MAY PROMOTE TOOTH REGENERATION

Since USAG-1 is known to be the antagonist of BMP and Wnt signaling pathways, scientists then investigated whether the removal of USAG-1 can promote the formation of additional teeth.

Evidence from USAG-1 Knockout Mice

Scientists target USAG-1 for tooth regeneration through the study of USAG-1 knockout mice. The USAG-1 knockout mouse is an experimental mouse that the USAG-1 is being disabled. This allows the scientists to examine results of mice without the function of USAG-1. Studies of mice without the USAG-1 gene shows that mice can form extra normal teeth. By reducing the USAG-1 gene, the signal of BMP and Wnt increased and reduced cell apoptosis, which could allow the development of new extra teeth that are normally unattainable. The supernumerary teeth have complete normal structure just like other teeth. Therefore, this shows that USAG-1 can control the number of teeth (Takahashi et al., 2024). This result enhances the possibility of tooth regeneration.

Rescue of Rudimentary Tooth Germs

Further research suggested that one of the possible reasons for the formation of supernumerary teeth is due to the rescue of rudimentary tooth germs. In a mouse's mouth, diastema is a toothless region between incisors and molars. During the early development of mouse teeth, there are many tooth germs formed in diastema and the front part of the first molar. Some of the temporary germs developed to the bud stage. However, some of them disappeared through apoptosis. Many important signaling pathways of tooth development are found to be active in these germs. Even though these rudimentary germs develop in mouse embryos, they tend to disappear through apoptosis (Takahashi et al., 2020).

In the study of USAG-1 knockout mice, supernumerary are mostly found in diastema. This suggested that without USAG-1 the rudimentary tooth germs in diastema are rescued and continue to develop into normal teeth. USAG-1 blocked the BMP signaling. Without USAG-1, the signals of BMP increase, which reduces apoptosis. This allows the rudimentary tooth germs to continue to develop. Moreover, the experiment found out that BMP signaling is increased in USAG-1 knockout mice. Therefore, the stronger signaling allows the formation of supernumerary teeth (Takahashi et al., 2020).

Rescue of Arrested Tooth Development

Scientists also study if inhibiting the USAG-1 can rescue teeth that stop developing due to genetic factors. Many genes can cause congenital tooth agenesis. When a gene involved in the development of teeth is not functioning properly, it can cause the normal formation of teeth to pause, leading to humans being born with the absence of few permanent teeth. The scientists study the rescue of arrested tooth development

with mice. They found out that some genes, such as Runx2, Wnt10A, and EDA1, that cause congenital tooth agenesis are shared by mice and humans (Takahashi et al., 2020).
In Runx2 knockout mice, mice present congenital tooth agenesis. Mutations of the Runx2 gene are also linked to congenital tooth loss in humans. The scientists crossed USAG-1 knockout mice with Runx2 knockout mice in order to study the restoration of arrested tooth development (Takahashi et al., 2024). In the double knockout mice, the researchers found out the formation of teeth continues further than the Runx2 knockout mice (Takahashi et al., 2020). Also, the arrested tooth development was successfully rescued. Even though the study only examined the Runx2 gene, it proposed that the suppression of USAG-1 gene can help the formation of teeth that are affected by congenital defects (Takahashi et al., 2024).

Anti-USAG-1 Antibody Treatment and Third Dentition

USAG-1 knockout experiment helps the study of the function of USAG-1 in tooth development. Scientists then investigate the potential therapeutic approach for tooth regeneration. They developed anti-USAG-1 neutralizing antibodies. These antibodies bind to USAG-1, neutralizing the inhibitory effects on Wnt and BMP signaling pathways. Therefore, the signaling for tooth development can be more active, leading to potential rescue of rudimentary tooth germs and arrested tooth development (Takahashi et al., 2024). The scientists tested these antibodies with EDA1 knockout mice, which have congenital missing lower third molars. After the treatment of anti-USAG-1 antibody, the mice without EDA1 show a development of lower third molars. Furthermore, the effects depend on the dose of the antibody. The results of tooth regeneration are shown both in EDA1 knockout mice and normal mice. This experiment suggests that USAG-1 targeting antibodies can reduce congenital tooth agenesis and promote tooth regeneration in the knockout mouse models. Scientists also tested mice without other genes that have congenital tooth loss. The results show that inhibiting the USAG-1 can affect the number of teeth and size (Takahashi et al., 2024).

Scientists also proposed that anti-USAG-1 antibody treatment as a potential treatment for not only congenital tooth agenesis but also acquired tooth loss, even though its effectiveness in humans has not yet been established. Humans normally only have two dentitions: baby teeth and permanent teeth. The third dentition structure tends to regress due to apoptosis. However, researchers found that humans may have the ability to naturally form third dentitions. They observed patients with supernumerary teeth and suggested that they might come from third dentition (Takahashi et al., 2024). Furthermore, the study of ferrets with anti-USAG-1 antibody treatments developed teeth similar to third dentition. Scientists considered them as third dentition because they form after the permanent teeth and have similar shape to the teeth before them. This is a crucial finding since ferrets and humans have similar dental patterns (Takahashi et al., 2024). However, it's uncertain whether humans will develop a third dentition with anti-USAG-1 antibody treatment.

EXPRESSION AND FUNCTIONS OF USAG-1 GENE IN NON-DENTAL TISSUES

Expression of USAG-1 in Non-Dental Tissues

USAG-1 is not only expressed in dental tissue but also in several parts of the human body. According to Tong et al. (2022), USAG-1 is also expressed in several non-dental tissues, including the skin, intestines, brain, lungs, kidneys, and vasculature. This suggests that USAG-1 also plays a role in other biological processes rather than only tooth development. Since USAG-1 is the antagonist of BMP and Wnt signaling pathways, the inhibition of USAG-1 can potentially affect other organs instead of only dental tissues. As a result, the study of inhibiting USAG-1 as a treatment for tooth regeneration should consider the effect on other parts of the human body.

Role of USAG-1 in the Kidney

USAG-1 is observed to be highly expressed in humans' kidneys. It was found to be mostly expressed in epithelial cells of the distal collecting ducts. Furthermore, USAG-1 is the antagonist of BMP7 in the kidney. BMP is important for the normal development of the kidney. It can protect the kidney by alleviating kidney injuries. It reduces the apoptosis of kidney tubular epithelial cells and reverses kidney scarring. However, the USAG-1 antagonizes BMP7, which interferes with the protective effects of BMP7. Hence, with anti-USAG-1 treatment, it can be a possible benefit for the kidney. In the experiment of USAG-1 knockout mice, USAG-1 knockout mice with kidney injury were observed to survive longer and have better renal function being preserved than wild-type mice (Li et al., 2021). Therefore, the inhibition of USAG-1 for tooth regeneration could have systemic effects that need further research.

ASSOCIATION OF USAG-1 WITH CANCER

In cancer studies, USAG-1 is usually referred to as SOSTDC1. SOSTDC1 has been associated with the development and progression of many cancer types, such as renal, gastric, breast, and thyroid cancers (Tong et al., 2022). Hence, these findings are important for understanding the potential effects of USAG-1 inhibition for tooth regeneration.

USAG-1 in Renal Cancer

Researchers investigated the role of SOSTDC1 in renal cell carcinoma. They examined its expression in normal kidney and kidney tumors. The scientists tested with two separate groups of patients with different methods. They observed similar results in the two independent groups, which both showed that SOSTDC1 is highly expressed in normal kidney but much lessened in kidney cancer (Blish et al., 2008). Most importantly, the scientists discovered that clear cell renal cancer with SOSTDC1 added inhibits the proliferation of kidney cancer cells.

In addition, knowing that SOSTDC1 acts antagonistically to BMP and Wnt signaling pathways, scientists inhibit Wnt and BMP pathways separately. They found out that the inhibition also prevents the proliferation, but SOSTDC1 has a stronger effect. This shows a possible relationship that SOSTDC1 inhibits Wnt and BMP signaling pathways, which reduces the proliferation of kidney tumors. Thus, SOSTDC1 may have a tumor-suppressing role in renal cell carcinoma (Blish et al., 2008).

USAG-1 in Gastric Cancer

In the study of SOSTDC1 in Gastric Cancer, scientists compared normal stomach tissue with tumors and metastatic tissue. They discovered that almost all normal tissues have the expression of SOSTDC1. On the other hand, in tumors and metastatic tissue, the expression level of SOSTDC1 is hard to detect (Cui et al., 2019). Furthermore, the scientists found that different levels of SOSTDC1 have different effects on gastric cancer. Higher levels of SOSTDC1 reduce cancer cell growth more than the lower levels one. In addition, SOSTDC1 is related to the motility of cancer cells (Cui et al., 2019). This finding suggests that SOSTDC1 may contribute to the suppression of tumor growth and spread.

USAG-1 in Breast Cancer

In the study of breast cancer, researchers compared breast tumors matched with normal breast tissue. They discovered that SOSTDC1 expressions are lower in the tumor tissues. SOSTD1 expressed lower in larger tumors than in smaller tumors. Also, patients with higher cancer stages have less SOSTDC1 level than patients with early cancer stages. In this breast cancer experiment, Wnt signaling was not affected by SOSTDC1. Whereas, SOSTDC-1 antagonizes BMP-7 but not BMP-2. This shows that the effects of inhibition of SOSTDC-1 can be varied by different cases. In this breast cancer experiment, the findings suggest that SOSTDC1 may protect against the progression of breast cancer (Clausen et al., 2011).

USAG-1 in Thyroid Cancer

In the study of SOSTDC1 in Thyroid, researchers compared thyroid cancer tissues with nearby normal thyroid tissues. They found out that the expression of SOSTDC1 is lower in tumor tissues. The tumor cell growth can be slowed down with cells that have more expression level of SOSTDC1. In larger and more advanced tumors, SOSTDC1 tends to be lower. The level of SOSTDC1 can affect the progression of thyroid cancer. Also, they found that SOSTDC1 can inhibit Rb-E2F pathways, which reduce cell proliferation. Furthermore, with the increased expression of SOSTDC1 in mice used for the study of thyroid cancer, the tumor size decreased noticeably. Hence, through these findings, SOSTDC1 may act as a tumor suppressor in thyroid cancer (Liang et al., 2015).

Interpretation of Cancer Studies

Throughout the study of USAG-1 gene in renal, gastric, breast, and thyroid cancers, they all show similar patterns. In tumor cells, they are found to have lower expression levels of USAG-1. Especially in the studies of larger and advanced stages of breast and thyroid cancers, the expression level of the USAG-1 gene tends to be lower. These findings all support the idea that USAG-1 may act as a tumor suppressor in some tissues. However, it was not suggested that the therapeutic USAG-1 inhibition increase the risks of getting cancer. The reduction of USAG-1 could be the consequence of cancer cells. The effects of USAG-1 vary on different cancers and signaling pathways.

POTENTIAL RISKS OF THERAPEUTIC USAG-1 INHIBITION

Potential Effects on Non-Dental Tissues

Since USAG-1 is known to be expressed in many organs of the human body, not only dental tissues, the treatment of anti-USAG-1 antibodies could potentially affect other parts of non-identical tissues. These effects could be beneficial. Given that USAG-1 has biological functions throughout the human body, scientists should consider the possible systemic effects when evaluating the safety of the tooth regeneration treatment.

Potential Cancer-Related Risk

In renal, gastric, breast, and thyroid cancers, USAG-1 expression level has been associated with the tumor cells development. It was found that the increased USAG-1 expression can reduce the proliferation of certain tumor cells. Since USAG-1 antagonizes Wnt and BMP signaling pathways, which are involved in the regulation of cell proliferation, the inhibition of USAG-1 can affect this function. In the studies of cancer, scientists examine or alter the expression level of the USAG-1 gene in tumor cells. On the other hand, anti-USAG-1 antibody treatment neutralizes the activity of the USAG-1 protein using antibody to regulate USAG-1. Hence, the two approaches may not lead to the same biological effects. Furthermore, there is a lack of direct evidence showing that the therapeutic USAG-1 inhibition could promote tumor progression or increase the risks of cancer development. As a result, the study of tooth regeneration treatment that inhibits USAG-1 should investigate the potential cancer-related risk.

Risk of Uncontrolled or Abnormal Dental Development

The reason scientists inhibit the USAG-1 gene is to increase the Wnt and BMP signaling pathways. This allows the arrested or rudimentary tooth germs to continue to develop. However, the study shows that the development of teeth requires precise regulation to control the teeth number, position, and shape. Research also suggested that Wnt signaling should be carefully balanced or it can interfere with the normal development of teeth (Hermans et al., 2021). Hence, the inhibition of USAG-1treatment for tooth regeneration should examine if the signaling pathways for tooth development is regulated properly or it can potentially cause uncontrolled or abnormal dental development.

Limited Human Evidence and Unknown Long-Term Safety

USAG-1 inhibition for tooth regeneration lacked long-term human study. Most of the research was conducted through using animal models. The results obtained from animal models can be different from the outcomes humans have. Researchers found out that the cellular composition and molecular characteristics of human teeth and mice teeth are different (Krivanek et al., 2020). Therefore, the effectiveness of the treatment might be different between animals and humans due to the distinct dental tissues. In addition, the results vary in different methods. In the knockout mice, the USAG-1 gene was being inactivated before birth. The effects of knockout mice start in the beginning of life and can be permanent. Whereas, the anti-USAG-1 antibody neutralizes the activity of USAG-1 protein. The effects of antibody treatment function in particular time and can be temporary. Also, every patient has different conditions. For instance, they may have different types of congenital tooth agenesis, such as hypodontia, oligodontia, and anodontia. They may have different causes for tooth loss. They can be born without teeth due to genetic factors or lose their teeth later in life. Different conditions can influence the effectiveness and safeness of the treatments.

Moreover, the long-term effect of the treatment on humans is not yet established. It remains unclear whether the future conditions of the regenerated teeth can maintain its function over time. Also, they need to check if there are delayed effects of inhibition of the USAG-1 on non-dental tissues (Moradi et al., 2026). Therefore, additional clinical research is essential for tooth regeneration treatment.

CONCLUSION

USAG-1 is known as the antagonist of Wnt and BMP signaling pathways. These pathways are important in the development of teeth. They are carefully regulated to develop correct teeth number and structure. Scientists use the USAG-1 knockout mice to study the function of USAG-1. When the USAG-1 is being inhibited, the signaling of Wnt and BMP increases. These signalings can reduce apoptosis and rescue the rudimentary and arrested tooth germs. The animal studies of anti-USAG-1 antibodies shows the potential treatment for congenital tooth agenesis and acquired tooth loss through the promotion of third dentition.

USAG-1 is not only expressed in dental tissues but also many organs in the human body. In the kidney, it also helps the regulation of Wnt and BMP signaling pathways. In the studies of renal, gastric, breast and thyroid cancers, USAG-1 is observed to have lower expression levels in tumor cells than normal cells. Moreover, in some cancers, the increase of USAG-1 expression level can reduce the tumor cells proliferation. Across these studies, USAG-1 has been associated with a tumor-suppressor role. Hence, through these findings, the inhibition of USAG-1 for tooth regeneration might also affect nondental tissues and the progression of cancers.

The inhibition of USAG-1 shows a potential approach for tooth regeneration. The animal models studying USAG-1 provide the evidence for the biological mechanism of tooth regeneration through anti-USAG-1 neutralizing antibodies. However, the potential therapeutic risk is not fully studied. Also, human evidence

is limited and the study of long-term effects is not yet discovered. As a result, further research for the safety of the treatment is needed to make the inhibition of USAG-1 become an approach for tooth regeneration.

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