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Review Article

USAG-1 Inhibition: Paving the Way for Lab-Grown Tooth Regeneration in Modern Dentistry

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ABSTRACT

Tooth loss is a prevalent health issue that traditional solutions address through either prosthodontic restorations or dental implants. Laboratory-produced bioengineered teeth are no longer a scientific speculation, as regenerative medicine continues to make innovative progress. The critical advancement within this research area relies on USAG-1 (Uterine Sensitization Associated Gene-1) gene suppression which blocks tooth development. Scientists have shown that USAG-1 inhibition leads to supernumerary tooth growth through recent studies thereby creating a modern dental therapeutic option. The investigative analysis reviews existing knowledge about lab-grown teeth to explore USAG-1 regulation of dental tissue regeneration together with potential treatments despite implementation barriers.

Keywords: Bioengineering, Gene Editing, Regenerative Dentistry, Tooth Regeneration, USAG-1 Inhibition

BACKGROUND

Tooth loss is a severe social health problem globally whose origins can be traced to numerous factors, such as traumatic events, periodontal diseases, and birth malformations [1]. The tooth can be fractured or lost completely by the traumatic injuries like accidents or sport incidents and the periodontal diseases can also cause the progressive loss of gums and other bone structures that support the tooth and result in the loss of the tooth [2]. Also, a hereditary disorder like hypodontia, in which a person is born with missing teeth, also plays a role in the tooth loss in the entire world. All these types of tooth loss pose significant challenges to patients, both aesthetically and functionally, i.e. the elderly find it difficult to chew, talk and smile without fear [3].

After these difficulties, traditional solutions, such as dentures, braces, and dental implants have been developed. There are significant limitations to these methods though. Dentures and braces can be used to replace missing teeth, but no longer address the loss of bone that frequently occurs after removing teeth that lead to bone loss and bone erosion [4]. Dental implants carry a risk of complications such as peri-implantitis, infections and implant failure in severe cases particularly in patients with low bone density or compromised healing abilities [5].

Such restrictions have necessitated the development of better and improved solutions in the area of regenerative dentistry. Regenerative dentistry is a new branch which focuses on the restoration of natural tooth structures by encouraging the natural regenerative potential of the tooth. Regenerative dentistry aims to exploit the potential of biological pathways to achieve fully functional and natural teeth, contrary to other traditional approaches that use external prosthetics or implants [6]. In this technique the full tooth structures are bioengineered such as roots and supporting tissues to produce a solution that replicates the normal development of teeth. The use of genetic solutions to induce tooth regeneration has been one of the most promising directions in this field and can present a permanent and biologically incorporated solution [7].

Among the host of the genetic targets, that are currently in consideration is the Uterine Sensitization Associated Gene-1 (USAG-1), which may be said to be an important factor in the formation and posterior development of teeth. USAG-1 is an extracellular protein that inhibits crucial signaling systems regulating tooth formation, i.e. the bone morphogenic protein (BMP) signaling pathway and the Wnt signaling pathway [8]. Here are the pathways which take place during the process of development of the teeth i.e. odontogenesis. Scientists have identified how to control the regulation of the USAG-1 gene to prevent or ablate this gene can trigger tooth repair through natural acquisition of a juvenile or adult mammal by stimulating the formation of teeth [9].

Controlling expression of USAG-1 offers an unprecedented possibility as regenerative therapies are involved and, hopefully, will eventually lead to the elimination of the need to use dental implants and other artificially manufactured structures. Recent researches have shown that by stopping USAG-1 production, an additional tooth can be produced and that an identical process can be employed to regenerate missing teeth in humans. This has dramatic consequences not only in treating diseases that are inherent, like hypodontia, but also in patients who have lost teeth in trauma or by disease [10].

Scientists have been discovering more ways through which teeth can be repaired using this gene without causing one to go through a major medical procedure, which can be regarded a non-surgical type of treatment that can transform the entire face of dentistry [11]. Thus, the purpose of the review is to examine what is known about the research on the USAG-1 inhibition and how it can transform tooth regeneration with regard to its therapeutic value, challenges and future possibilities of lab-grown teeth as an alternative to regular dental therapies

REVIEW

History of USAG-1 and its role in the formation of the teeth: The Uterine Sensitization Associated Gene-1 (USAG-1) was discovered during studies about gene regulation in developmental biology. USAG-1 was first discovered as an important regulator of mammalian tooth development and plays a role in suppressing tooth formation during early embryonic development [12]. The gene has a protein secreted that is negative regulation of two key signaling pathways; Bone Morphogenic Protein (BMP) and Wnt signaling. These signaling pathways are critical to the odontogenesis or formation of teeth. The role of USAG-1 was initially identified as researchers noticed that the expression of it suppressed tooth development by preventing BMP and Wnt signaling, both of which are necessary in tooth bud formation [13].

Preliminary experiments in mice suggested that this destruction of USAG-1 expression during embryonic development resulted in the natural generation of teeth. The result prompted the consideration of the possibility of taking advantage of USAG-1 manipulations as a way to restore teeth, which would be a novel method to avoid the use of conventional dental prosthetics [14].

The rise of USAG-1 in Tooth Regeneration: The role of USAG-1 in tooth development is not new, but it was only many years later, when gene-editing and antibody therapies were developed, that the application of USAG-1 became more widely recognized in tooth regeneration. When scientists started to explore the regenerative medicine in more detail, the USAG-1 as a potential

genetic target to trigger tooth growth became a popular topic of discussion [15].

In a study, the regeneration of teeth was also possible when the SOSTDC1 gene was knocked out to express USAG-1 mouse embryonic stem cellsIt is after this way of control that supernumerary teeth formation was realized and this was initial positive signal that USAG-1 inhibitory impact causes tooth growth. This study opened the door to use of USAG-1 blocking as nonsurgery procedure to repair lost-teeth in human beings. Based on this finding, scientists started to investigate the possibility to prevent USAG-1 by other, more practical methods like monoclonal antibodies [16].

The finding of the ability to silence the expression of USAG-1 under specific therapy preceded this change in interest to study the therapeutic development. The inhibition up to the USAG-1 very soon became one of the hottest regenerative dentistry genetic methods. With scientists starting to study antibody therapies or gene-editing approaches, including CRISPRCas9, to either activate or silence the gene, the USAG-1 gene started taking center stage in regenerative dental research [17].

DISCUSSION

In 2007-2008, researchers at Kyoto University came across a breakthrough in understanding this when they discovered that in mice lacking USAG-1 gene (gene that produces a tooth suppressing protein) more teeth were growing in the mice. This finding supported the role of USAG-1 in controlling emanation of teeth. Following this result, in 2018, a research team at Kyoto University has made a monoclonal antibody capable of inhibiting the USAG-1 protein.

They also managed to demonstrate that this antibody could make the teeth develop in mice and ferrets which is a big jump in the dentistry regeneration field [8].

Research published in 2021 found the administration of the USAG-1-blocking antibody to promote tooth regeneration as an effective and potentially promising alternative in the treatment of the human mouth. Toregem BioPharma, a start-up that Dr. Takahashi is a cofounder of, announced in May 2024 the official beginning of human clinical trials, which represents a significant step towards translating laboratory results into practice [19].

The clinical trials commenced in October 2024 at Kyoto University Hospital in 30 healthy adult men who had at least one missing tooth. The initial one, which will take 11 months, is aimed mainly at assessing drug safety. After the first stage is completed, researchers will start a second stage of trials with children aged 2 to 7 years with congenital tooth agenesis. Should the trials turn out to be successful, around 2030, the treatment could be offered to the general population and represent a new step in tooth regeneration therapy [20].

CONCLUSION

To conclude, it can be asserted that the inhibition of USAG-1 has a tremendous potential as a paradigm shift in regenerative dentistry, which promises natural tooth regeneration. Emerging developments such as positive results in animal research and initiation of human clinical trials are steps toward the realization of this novel treatment. USAG-1-based treatments would provide a viable alternative to conventional dental prosthetics in case of success. Further studies and clinical trials will play a significant role in establishing its future effects in the sphere of dental care.

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Sajda Khan Gajdhar : Contributed to the conceptualization, writing of the original draft, and submission of the manuscript.

ABBREVIATIONS USED IN THE STUDY:

a) **USAG-1:** Uterine Sensitization Associated Gene-1
b) BMP: Bone Morphogenic Protein
c) Wnt: Wingless-related integration site
d) CRISPR-Cas9: Clustered Regularly Interspaced Short Palindromic Repeats-Cas9

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