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Tooth regeneration using USAG-1 gene: a review *

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Abstract

A groundbreaking teeth regeneration drug, developed by Japanese researchers, suppresses tooth growth, offering a potential alternative to dentures and other dental prosthetic replacements. Clinical trials begun recently, with promising outcomes expected. This innovative therapy could revolutionise dental care for patients with missing teeth.

Keywords: USAG-1; tooth regeneration

Introduction

Dental caries and periodontal diseases are one of the most common causes of missing teeth. Congenital edentulism can be attributed to an incidence of 1% (1). Prosthetic replacement of natural teeth using dentures or dental implants is considered as standard treatment procedure. In recent few years, pre-emptive medicine for tooth regeneration by applying tissue engineering techniques have been reported in various studies. However, various issues such as high cost, tumorigenicity, safety and ethical concerns have been raised with current tissue regeneration approaches. Further to this, new technologies in the form of molecular targeted therapy has been developed using genomic analysis, research epidemiology and mouse model studies (2).

Katsu Takahashi, a Japanese researcher, has developed a drug that can regrow teeth by suppressing the USAG-1 gene, which inhibits tooth growth. USAG-1 is a bone morphogenetic protein (BMP) antagonist (3). Murashima-Suginami A and co-workers demonstrated that USAG-1 deficient mice showed increased BMP signalling, preventing apoptosis which eventually led to formation of supernumerary teeth (4). These pathbreaking discoveries aim to help individuals with congenitally or acquired missing teeth, offering an alternative to dentures and implants (5).

The groundbreaking discovery of the drug that can re-grow teeth was first reported in Osaka (Japan), with the clinical trials launched in October 2024 at Kyoto University Hospital. The research team, led by Katsu Takahashi, had been working on this innovative treatment modality since many years (6).
The drug is described as an antibody-drug that inhibits the USAG-1 protein, which is known to suppress tooth growth. Researchers have also explored other drugs, such as Tideglusib, which has shown promising results in stimulating tooth re-growth and repairing cavities (7). Tideglusib is a drug that may help repair tooth damage by stimulating stem cells in the tooth pulp. It's a small molecule that's been used in clinical trials to treat Alzheimer's disease (8).

Third set of teeth

The concept of a "hidden" third set of teeth in humans is based on the idea that our ancestors might have a third set of teeth, but this trait was lost during the evolution. While there isn't direct conclusive evidence of third set of teeth in modern humans, there are certain evidence from the field of palaeontology, comparative anatomy and developmental biology that suggest our ancestor may have had additional teeth. While humans do not typically develop a third set of teeth, there are some interesting exceptions in the form of supernumerary teeth, such as mesiodens, paramolars, distomolars and even in the form of odontoma. The mechanism behind supernumerary tooth formation have recently been studied. The third dentition begins developing after the second successional lamina is formed from the developing permanent tooth in human being and regresses after cell death like in the case of rudimentary incisor teeth of the mouse (9).
In humans, certain rare condition viz., Cleidocranial dysplasia or Nance-Horan syndrome, where an individual develops an extra number of teeth, that may exceed 30 teeth (10). Such scenarios suggest that genetic potential for development of additional teeth is still present in our genome.
During the Palaeozoic era, around 450 million years ago, vertebrates had multiple set of teeth that were replaced throughout their lifetime, in the form of a process, called "tooth replacement". This allowed for the maintenance of sharp, functional teeth, that can still be found in some animals like sharks.
As vertebrates evolved, the number of set of dentitions decreased, and the complexity of tooth structure increased (11). In mammals, the dental pattern typically consists of two sets of teeth: deciduous (primary) teeth and permanent teeth.
As previously mentioned, scientific studies suggests that the genetic machinery for developing multiple sets of teeth still seems to persist in our genomics. Studies have identified numerous genes like Mmp20, Fgf8, Dlx1, P63, Pax9, Amelx, Edar, Msx1, Dspp, etc. involved in tooth development, including those that regulate tooth number, size and shape (12).

USAG-1 gene

USAG-1 (Uterine Sensitization-Associated Gene 1) is a gene that has been recently found to have a role in the regulation of tooth development and growth. This gene is a member of the heparan sulphate proteoglycan family and has predominantly shown to have a key role in the regulation of cell growth and differentiation.
Studies have shown that USAG-1 is expressed in the dental lamina and tooth bud during stages of tooth development. It is involved in regulation of morphogenesis, especially in the formation of the tooth bud and cap stages. USAG-1 has also been shown to regulate the expression of key tooth development genes, including Msx1 and Pax9. Gene USAG-1 is located on Chromosome 1q32, in humans. Its function is to inhibit Wnt/β-catenin signalling pathway, that is known to regulate cellular processes.
By inhibiting Wnt/β-catenin signalling, USAG-1 helps to:
- Regulate tooth morphology
- Control number of teeth and interdental spacing
- Modulate the growth and development of dental tissues

In their study, Honoko Kiso and co-workers reported BMP-7 and USAG-1 were expressed in late bud and early cap stage of tooth development of mice. The elimination of USAG-1 saved the apoptotic elimination of odontogenic mesenchymal cells. USAG-1 was shown to act as BMP-7 antagonist. The researchers concluded that activation of USAG-1 could be used to stimulate formation of third set of teeth (13).
Thus, USAG-1 may provide a new tool for the study of tooth development and regeneration, allowing scientists to better undermine the complexity of cellular and molecular mechanisms involved in these processes (14).

Possible risks

There are chances of resultant abnormal tooth morphology due to manipulation in tooth development pathways. This can typically lead to

formation of fused teeth or supernumerary teeth. Inhibition of USAG-1 gene may cause tissue overgrowth, overcrowding, root resorption, or malocclusion. Major issue may occur w.r.t proper integration with surrounding tissues, leading to instability, increased risk of tooth exfoliation stemming from tooth mobility. Abnormal tooth development or altered nerve growth may lead to sensory disturbances, such as tooth sensitivity, pain, or altered sensation.

There can be consequences such as mutations or epigenetic changes that may have impact on overall health of an individual. Altering cell growth and differentiation pathways can markedly increase the risk of cancer, due to uncontrolled cell proliferation, causing tumorigenesis.

As USAG-1 is involved in other physiological processes as well, inhibiting it may result into, diseases of bone metabolism, renal or cardiovascular system. Introducing any new growth factor or inhibiting a gene may even trigger an adverse immune response, leading to inflammation, or tissue damage. There are also risk of mutagenesis, undirected differentiation and tumour formation (15).

Minimizing risks

To minimize probable risks associated with the inhibition of USAG-1, researchers and clinicians will need to investigate its long-term effects on tooth development and overall health. By ensuring precise targeted delivery of the USAG-1 inhibitors, there can be minimal side effects. Regular assessment of patients for signs of adverse reactions, shall be mandatory.

By addressing risks, scientists and clinicians can work collaboratively towards developing safe and effective treatments outcome by USAG-1 gene inhibition. Safety measures can be taken into consideration by performing more in vitro and in vivo trials of tissue engineering and regeneration therapies (16).

Conclusion

USAG-1 plays a crucial role in regulation of tooth morphogenesis, especially in the formation of the tooth bud and cap stages. It also regulates the expression of key tooth development and regeneration genes. The discovery of USAG-1's role in tooth development and regeneration has significant implications for our understanding of these complex processes and may provide a new target for the development of therapies aimed at promoting tooth regeneration and repair.

Declaration of Interest

None

Author Contributions

Resham Pakhmode: Data acquisition and interpretation, literature search and manuscript preparation as well as editing.

Vivek Pakhmode: Data acquisition, definition of intellectual content, literature search, and manuscript preparation.

Statement on the use of artificial intelligence in manuscript preparation

Artificial intelligence was not used in the preparation of this manuscript.

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