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Tideglusib – A Wonder Molecule for Dentin Repair

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Abstract:
Tideglusib is a drug which has been used for treatment of Alzheimer's disease, recent studies have shown effect of drug in dentin repair by inhibiting Glycogen synthase kinase enzymes. It has also been shown to be better that Mineral trioxide aggregate which is currently used material for dentin remineralisation.

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I. Introduction

Dentine is a vital tooth mineral that is produced by highly specialised mesenchymal cells called odontoblasts.. It protects pulp tissue from microbial and other noxious stimuli, provides essential support to enamel and enables highly mineralized and fragile enamel to withstand occlusal and masticatory forces without fracturing.(1)

When tooth mineral is compromised either following trauma or infection (caries), the inner cellular soft pulp tissue can become exposed to the external environment and become infected. When the soft inner pulp tissue is exposed, a natural repair process is activated that involves the mobilisation of resident mesenchymal stem cells to differentiate into new odontoblast-like cells that secrete a form of tertiary (Reparative) dentine. (2) This stem cell activation is dependent on Wnt/β-catenin signaling, which is upregulated following tissue damage, and the level of reparative dentine produced is directly related to the level of signaling activity (Clevers and Nusse 2012; Hunter et al. 2015; Babb et al. 2017; Neves et al. 2017)(6)

Reparative dentine bridge forms as a response to external irritation in order to increase the thickness of the mineralized tissue barrier between the oral microbes and the pulp tissue and protect the pulp from infection by sealing the tooth pulp from the external environment.(1)

Natural reparative dentine formation is insufficient to effectively repair large lesions, involving the loss of dentine after caries removal. Several pulp-capping materials, including calcium hydroxide and hydraulic calcium-silicate cements ,such as mineral trioxide aggregate (MTA), are used to fill the tooth and replace the lost dentine.

Wnt/β-catenin signaling Pathway

Wnt signaling is an evolutionarily conserved pathway that regulates many crucial aspects of embryonic development and adult homeostasis such as cell fate determination, migration, polarity and organogenesis. This pathway also regulates expression of many tumor-related proteins and typically shows abnormal activation in various cancer cells. Activation of Wnt/ β-catenin signaling has been demonstrated as an early response to damage in many tissues that can induce the repair process.(7)

In this pathway, Axin2 is a negative regulator and a down-stream target. Glycogen synthase kinase 3 (GSK3) is a key enzyme of this pathway and a proline/serine protein kinase ubiquitously expressed and involved in many cellular signaling pathways controlling metabolism, differentiation, immunity,as well as cell death and survival. In the presence of Wnt ligands, GSK-3 activity is inhibited, β-catenin can enter the nucleus

to interact with Lef/Tcf transcription and express the target genes such as Axin2. In the absence of Wnt ligands β-catenin and Axin2 are phosphorylated that leads to their ubiquitination and degradation.[7]

Glycogen synthase kinase-3 (GSK-3) is an essential human kinase, and it has been studied as a potential therapeutic target in many disorders, including neuropsychiatric disorder, depression, anxiety, schizophrenia, neurological, supranuclear palsy Parkinson's disease,

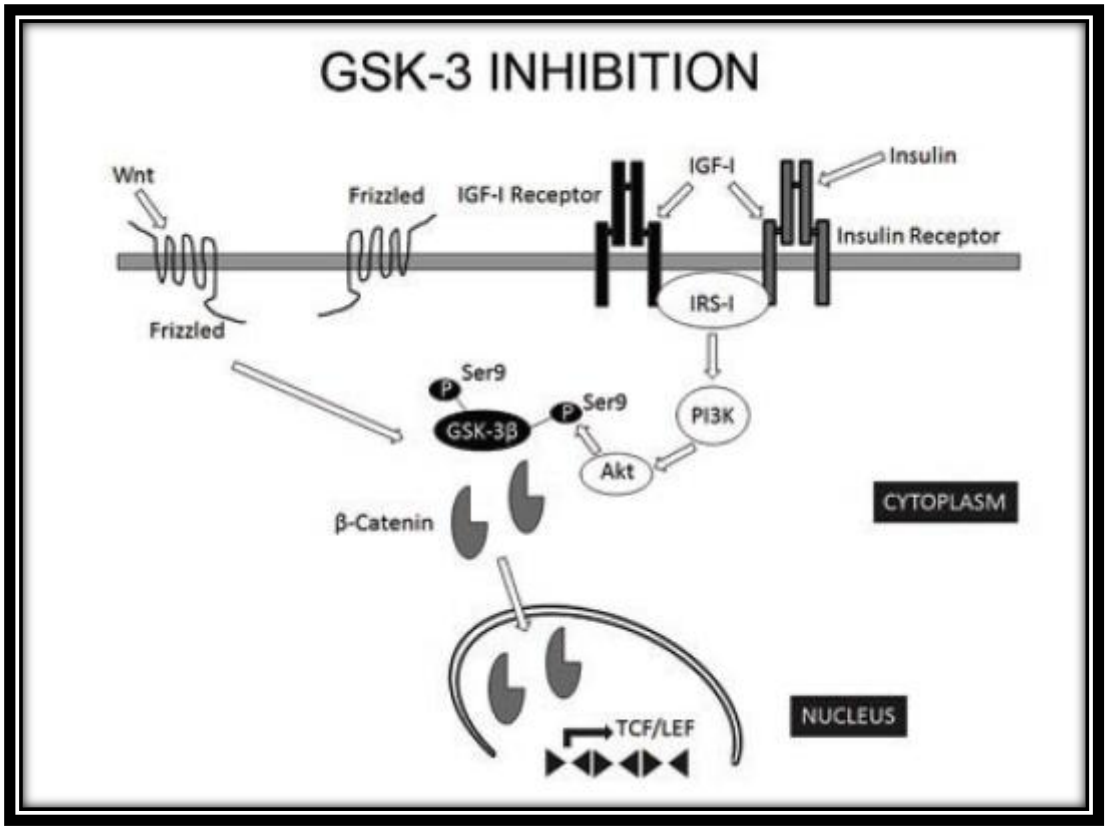

FIGURE 1 : Wnt PATHWAY ON GSK 3 INHIBITION

stroke, traumatic brain injury spinocerebellar ataxia type 1 inflammatory diseases, asthma, arthritis and various types of cancers.[2]

GSK3 inhibitors have various forms and can have natural or synthetic sources that exhibit different mechanisms of action. They can be ATP-competitive inhibitors, non-ATP-competitive inhibitors, and substrate-competitive inhibitors. Inhibition of GSK3 is a prime focus for targeting neurodegenerative and psychiatric disorders as well as behavioral impairments in Alzheimer's disease. A significant role of GSK-3 is its capacity to modulate human stem cells *in vivo*. Sato et al. showed that GSK-3 inhibition activates the Wnt pathway, thus promoting reparative dentine formation.

In dentistry repair process is accompanied by rapid increase of Axin2 expression and differentiation of Axin2 expressing cells into odontoblast-like cells that will subsequently form reparative dentin. Several GSK3 inhibitors have been shown to promote dentin repair in mice and rats with experimental pulp exposures.[7] Of these, Tideglusib is the only GSK3 antagonist drug that has to date been shown to be safe in patients.

Tideglusib for Dentine Repair

Tideglusib is a drug used for the treatment of Alzheimer disease and neuropsychiatric disorders. It is 4-Benzyl-2-(naphthalen-1-yl)-[1,2,4]thiadiazolidine-3,5-dione, which belongs to thiadiazolidinone group. Recent animal studies on 'Tideglusib' have shown to have an effect on dentin regeneration by inhibing GSK 3.

A study by Neves et al. evaluated the potential for natural tooth repair by using Tideglusib soaked in biodegradable collagen sponges placed directly into experimentally created deep cavities of mice molars in contact with the pulp. MTA was also placed as direct capping material on contralateral molar in this experiment.The sponge and MTA was sealed using Glass ionomer cement . This was left for 4–6 weeks before removal.

Micro-computed tomographic (μ CT) scanning was used to visualise and quantify mineral deposition at the drill site. Analysis at both 4 and 6 weeks revealed increased mineralisation with both Tideglusib and MTA. Overall the mineralisation was 2 times greater than in the sponge than with MTA treatment. The new dentine formed with the new conditions presented as dense dentine localised centrally to the injury site, revealing no remaining collagen sponge where the dentine was formed. Interestingly, by 6 weeks of treatment, the reparative dentine secreted when teeth were treated with Tideglusib filled the whole injury site from occlusal to pulp chamber roof,and the dental pulp remained vital.[(3)]

There have been studies in recent years suggesting potential tumorigenic effect of GSK-3 inhibition, to whom drugs had been systemically administered. However, in the abovementioned study (Neves et al., 2017), the doses needed for tooth repair were around 1,000 times lower, compared to those used in the clinical trials for neurological disorders (Neves et al., 2017).

It needs to be noted that an intra-dental application might lead to an increased release time of the drug, potentially causing significant local effects. Therefore, before allowing the usage of this drug, which alters numerous critical regulatory pathways, larger scale studies, should be performed to assess correctly the risk profile associated with its use; in turn, prospective patients should be properly informed to be able to take a genuinely informed decision, without which patients will not have enough relevant data for such a decision.

A potential treatment for cavities with Tideglusib (or other GSK-3 molecules) is in its early stages, as the results have only been confirmed on mice; however, the extrapolation of the results to human subjects should be done only after a proper efficacy on animal models has been completely established.

II. Conclusion

Promising potential for translational research approaches has been highlighted by use of tideglusib in animal studies. This property needs to be tested in human subjects respecting the ethical and regulatory criteria. Large scale clinical trial to explore the efficacy and safety of tideglusib in dental practice need to be designed and executed.

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