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Review

TISSUE ENGINEERING WITH STEM CELL FROM HUMAN EXFOLIATED DECIDUOUS TEETH (SHED) AND COLLAGEN MATRIX, REGULATED BY GROWTH FACTOR IN REGENERATING THE DENTAL PULP

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Abstract: A single paragraph of about 200 words maximum. For research articles, abstracts should Maintaining dental pulp vitality and preventing tooth loss are two challenges in endodontic treatment. A tooth lacking a viable pulp loses its defense mechanism and regenerative ability, making it more vulnerable to severe damage and eventually necessitating extraction. The tissue engineering approach has drawn attention as an alternative therapy as it can regenerate dentin-pulp complex structures and functions. Stem cells or progenitor cells, extracellular matrix, and signaling molecules are triad components of this approach. Stem cells from human exfoliated deciduous teeth (SHED) are a promising, non-invasive source of stem cells for tissue regeneration. Not only can regenerate dentin-pulp tissues (comprises of fibroblasts, odontoblasts, endothelial cells, and nerve cells), but SHED also possesses immunomodulatory and immunosuppressive properties. Collagen matrix is a material of choice to provide structural and microenvironmental support for SHED-to-dentin pulp tissue differentiation. Growth factors regulate cell proliferation, migration, and differentiation into specific phenotypes via signal-transduction pathways. This review provides current concepts and applications of tissue engineering approach especially SHED in endodontic treatment.

Keywords: Dentin-pulp complex regeneration; Signalling molecules; Stem Cell from Human Exfoliated Deciduous Teeth (SHED); Tissue engineering.

1. Introduction

Tissue injury can occur when it is exposed to various stimuli including microbial infections, mechanical damage (fractures, cracks, thermal factors), and chemical damage. This condition can cause cell apoptosis or necrosis, as well as microvasculature and stroma damage, leading to activation of inflammation and wound healing mechanism. During wound healing, mesenchymal stem cells are recruited to the site of injury to differentiate into stromal cells and replace damaged cells. However, if severe inflammation occurs in the dental pulp, the damaged cells cannot be effectively replaced or healed, a condition called irreversible pulpitis. In this condition, endodontic treatment must be carried out to remove the damaged pulp and prevent spread of the damage.[1–4]

Endodontic treatment involves partial or complete pulp removal (pulp extirpation) and filling the empty root canal with artificial material. Even so, the endodontic treatment causes the tooth to become more fragile, susceptible to caries and periapical infection and more likely to fracture as the tooth losses its vitality due to the absence of blood supply and innervation.[5–11]

Therefore, it is crucial to maintain the vitality of the pulp. A tooth without a viable pulp loses its defense mechanism and regenerative ability, making it more prone to severe damage and ultimately leading to extraction. Dentin-pulp complex reconstruction is an ideal approach to restoring pulp vitality by using mesenchymal stem cell or progenitor cells and signalling molecules added to the extracellular matrix to recover fibroblasts, odontoblasts, endothelial cells and nerve fibres functions.[8,10–14] Stem cells can be obtained from various tissues, including teeth, buccal mucosa, skin, fat, and bone.[15,16] The pulp of deciduous teeth, rich in stem cells known as stem cells from human exfoliated deciduous teeth (SHED), is a promising, easy to get, and noninvasive source of stem cells for

tissue regeneration.[17–21] Not only has the regenerative ability to generate dentin-pulp tissues, but SHED also possesses immunomodulatory and immunosuppressive properties.[20,22]

Scaffolds are 3-dimensional microstructural materials that provide a biological environment and structural support to facilitate cell growth, desirable interactions, and the formation of functional tissues.[8,23,24] One popular scaffold material is collagen. Collagen is a natural extracellular matrix built from protein and abundant in hard and soft tissues.[23] Collagen is biocompatible, permeable, and biodegradable, so it can function in helping migration, adhesion, proliferation, and cell differentiation.[8,12]

Growth factors are polypeptides that plays a very important role in the signaling process that occurs during tissue formation and regeneration of the dentin-pulp complex.[25,26] In the dentin-pulp complex regeneration, several Growth Factors work together through different signalling mechanisms, including *Transforming Growth Factor* β (TGF β), *Vascular Endothelial Growth Factor* (VEGF), *Bone Morphogenic Protein* (BMP), *Fibroblast Growth Factor* (FGF), *Platelet-Derived Growth Factor* (PDGF), and *Nerve Growth Factor* (NGF).[25,27,28] Growth factors will bind to cell surface receptors that subsequently induce cellular processes such as cell proliferation, angiogenesis, neovascularization, and all important steps in the regeneration process.[28,29]

Growth Factor plays a role in various stages of the healing process and tissue regeneration, including cell migration, angiogenesis, and neurogenesis.[26] It can also induce odontogenic differentiation through ALK5/Smad2/3, TAK1, p38, and MEK/ERK signalling pathways, supporting cell proliferation and collagen formation.[30,31] Tissue engineering application in endodontic treatment is expected to replace damaged or lost tissue with new natural pulp tissue and reduce the use of artificial materials, making teeth fully functional again.[14]

Tissue Engineering (TE) in Endodontic Treatment

As mentioned before, one challenge in endodontic treatment is maintaining dental pulp vitality and preventing tooth loss. Regenerative endodontics can overcome this hurdle.[32] According to "The American Association of Endodontists", regenerative endodontics is a procedure designed based on biological principles to physiologically replace damaged tooth structures, including root and dentin structures, as well as cells in the pulp-dentin complex.[10,32–34]

There are two concepts in regenerative endodontics, namely:[35] (1) Guided Tissue Regeneration (GTR), also known as the revascularization or revitalization approach, and (2) Tissue engineering (TE), an interdisciplinary approach to repairing damaged tissue using by combining three components: (1) cells (especially, stem cells) capable of forming pulp tissue, root dentin, and tooth-supporting tissues, (2) scaffolds to facilitate cell proliferation and differentiation, and (3) bioactive molecules (generally growth factors).[28,35–38]

Stem Cells

Stem cells are unique cells that possess self-renewal and differentiation properties into another cell type. Based on their differentiation potency, stem cells are divided into:[39–42]

- Totipotent Stem Cells

Totipotent stem cells are stem cells that can generate all types of cells and tissues that exist in organisms, usually can be obtained from embryonic stem cells (1-3 days old embryo). Totipotent cells

have the highest differentiation potential and allow cells to form embryonic and extra-embryonic structures. An example of a totipotent cell is the zygote, formed after a sperm fertilizes an egg. These cells can later develop into one of the three germ layers or form the placenta. After about four days, the cell mass in the blastocyst becomes pluripotent. This structure is a source of pluripotent cell.[35,43]

- Pluripotent Stem Cells
  Pluripotent stem cells are stem cells that can generate most cell types (over 200) and tissues found in organisms and have the ability to differentiate into cells of ectodermal, mesodermal, and endodermal origin. It can be obtained from a 5-14 day old blastocyst.[35,44,45]

- Multipotent Stem Cells
  Multipotent stem cells are stem cells that can generate a limited number of cell and tissue types depending on their origin. These cells can be obtained from cord blood, fetal tissue and postnatal stem cells including dental pulp stem cells.[35,45,46]
- Unipotent Stem Cell
  Unipotent stem cells are stem cells that have the narrowest differentiation ability, which is only into one cell type, but are able to divide repeatedly.[43,45]
- Induced Pluripotent Cells
  Induced Pluripotent Cells are pluripotent stem cells formed by induction of multipotent cells or adult somatic cells with pluripotent factors such as Oct4, Nanog, Sox2, Klf4, and C-myc.[45,47]

There are two approaches to deliver stem cells into the root canal. The first approach is cell transplantation, where autologous or allologous stem cells are applied directly to the root canal. The major obstacle to this process is immune rejection of allologous stem cells. Second is cell homing where stem cells are sent to the injured area, this process is influenced by many factors, such as age, cell number, culture conditions, and method of application. This condition involves the use of chemotactic factors such as Stromal Cell Derived Factor (SDF)-1 are injected to the site of injury to induce stem cell migration from the periapical area to the root canal.[27,48]

Based on their stage of development and origin, stem cells can be broadly classified into:[32,35,41,47] (1) Embryonic Stem Cells, which are stem cells derived from embryos, mainly from blastocysts. These cells are capable of dividing and renewing themselves over a long period. (2) Adult stem cells, which are stem cells derived from postnatal tissue, can be isolated from various body tissues, such as bone marrow, adipose tissue, encephalon, epithelium, dental pulp, etc.

Tissue injury is always associated with the activation of the immune system or inflammatory cells, including macrophages, neutrophils, CD4+ T cells, CD8+ T cells, and B cells, triggered by cell apoptosis, necrotic cells, microvascular damage, and stroma.[40,49–51] Mesenchymal stem cells can regulate specific and non-specific immune systems by suppressing T cells and dendritic cell maturation, decreasing B cell proliferation and activation, inhibiting NK cell proliferation and cytotoxicity, and increasing T regulatory (Treg) cell formation.[49,50]

There are two mechanisms of stem cell immunomodulation: soluble factors secretion and cell-to-cell direct contact. Prostaglandin E2 (PGE2), indoleamine 2,3-dioxygenase (IDO), nitric oxide (NO), interleukin-10 (IL-10), Hepatocyte Growth Factor (HGF), and Transforming Growth Factor 1 (TGFβ1) are secreted factors that have immunomodulatory property. Cell-to-cell direct contact mechanism involves CD274 (programmed dead ligand 1), vascular cell adhesion molecule-1, and galectin-1 expression. These molecules reduce effector T cell proliferation and increase the proportion of regulatory T cells (Treg).[49,50,52]

Various stem cells can be found in teeth and their associate tissues, such as Stem Cell from Human Exfoliated Deciduous Teeth (SHED), Dental Pulp Stem cells (DPSC), Stem Cells from the Apical Papilla

(SCAP), Periodontal Ligament Stem Cell (PDLC), Dental Follicle Precursor Cell (DFPC), and Dental Papilla Cell (DPC),Dental mesenchymal stem cells (DMSCs), and dental epithelial stem cells (DESCs). For pulp regeneration purposes, SHED, DPSC, and SCAP have strong potential.[35,41,53–55]

Stem cells from Human Exfoliated Deciduous Teeth (SHED)

Stem cells from human exfoliated deciduous teeth (SHED) were first obtained by Miura et al. in 2003. SHED expresses cell surface markers STRO-1, CD10, CD29, CD 31, CD44, CD73, CD90, CD105, CD146, CD13, CD166, Nestin, DCX, -tubulin, NeuN, GFAP, S-100, A2B5, CNPaseNanog, Oct3/4 and SSEAs (-3, -4) and does not express CD14, CD15, CD19, CD34, CD45, and CD43.[41,56–59]

SHED has two major advantages compared to other stem cells derived from dental tissue: it is easier to gain through noninvasive procedure and has high proliferation rate.[34,41,56,60,61] SHED exhibits higher proliferation rate compared to Dental Pulp Stem Cells (DPSCs) and Bone Marrow derived Mesenchymal Stem Cells (BMMSCs).[41,45,58,62–64]

SHED possess higher potential in forming dentin-pulp complex cells, namely osteoblasts, chondroblasts, adipocytes, endothelial cells, nerve cells, and odontoblasts.[57,58,65–67] The ability of SHED to differentiate into odontoblasts is characterized through the expression of dentin matrix protein-1 (DMP-1) and dentin sialophosphoprotein (DSPP).[45,58] DSPP induces stem cells to odontoblast differentiation through SMAD 1/5/8 phosphorylation and nuclear translocation via the P38 and ERK1/2 pathways. DMP-1 involves maintaining dentin mineralization.[68,69]

As for the potential for neural regeneration, SHED show more intensive expression of neural differentiation markers than DPSCs, such as b-III-tubulin, and nestin, in neural induction cell culture.[37] SHED is also able to increase the angiogenesis process by forming vascular connective tissue structures, expressing and synthesizing VEGF.[70] This ability is crucial to maintain pulp viability as it can supply oxygen and nutrients needed for cell metabolism for tissue regeneration.[71]

SHED also functioned as an immunodulator by suppressing T helper 17 (Th17) cell function and upregulating CD206+ M2 macrophages.[57,62] SHED are able to induce the secretion of proinflammatory cytokines such as interleukin 1b (IL-1b), interleukin 6 (IL-6), interleukin 10 (IL-10), and tumor necrosis factor- a. SHED is also capable to inhibit lymphocyte CD178 expression, suppressing the proliferation of lymphocytes, and decreasing the secretion of IL-4 and IFN-g while sequentially increasing the number of T-reg cells.[37,72,73]

Collagen Scaffold

Scaffolds are required for regeneration or tissue engineering to facilitate cell growth and functions in the transplanted area.[74–76] Interaction of the cell with the extracellular matrix influences many signalling pathways that change cell behaviours, i.e. adhesion, proliferation, and differentiation.[76,77] Scaffolds can be made of both natural and synthetic materials. Nanoscale proteins are the primary natural scaffolding materials. Nanoscale proteins include collagen, fibronectin, and vitronectin. Synthetic polymers are popular materials because they are biocompatible, biodegradable, mechanically stable, and can be designed in a variety of compositions and shapes.[77,78] These properties enable polymers to biologically affiliate and mimic the natural cell-extracellular matrix.[76,79] Natural scaffolds, such as collagen, have better biocompatibility, whereas synthetic polymers can be

controlled for their physicochemical properties such as solubility, microstructure, and mechanical strength.[76,79]

Nanofibrous scaffolds are more popular than microfiber scaffolds due to their high surface area, interconnected porosity, and positively stimulating extracellular cell-matrix interactions.[76] Nanofibrous scaffolds are made in 3 methods, namely electrospinning, self-assembly, and separation phase.[77] Electrospinning knew as the most tissue engineering application method frequently used to synthesize collagen or synthetic scaffold and/or transport system for the drug.[76]

Collagen is a hydrogel material with high biocompatibility; viscoelasticy similar to soft connective tissue; transport of nutrients and waste, uniform cell encapsulation, in situ gelation ability, and compatible to be modified by biofunctional molecules or growth factors.[80] Collagen contains arginine-glycine-aspartic acid (RGD) adhesion ligands, which enable cell-biomaterial interactions leading to cell adhesion.[75] Collagen matrix is compatible for dental pulp stem cells proliferation, adhesion, and differentiation as shown by formation of capillary like microvessels.[76,81,82] Two commercial injectable scaffolds, self-assembling peptide hydrogel and rHCollagen type I had been evaluated. It was found that both of those scaffolds promote SHED cell survival and when injected into the root canal, these materials promoted of odontoblast putative markers expression.[83]

Different collagen materials are compared such as collagen type I and III, alginate, and chitosan generating a good result in the proliferative and mineralizing activity of type I collagen. After implanting these cells, the formation of vascularized pulp-like tissue, odontoblast-like cells, and new dentin is produced. SHED onto PLA cells in dentinal discs.[80]

Collagen is a biocompatible material that can be degraded by enzymes; however, natural polymers are difficult to produce and may transmit pathogens from animals (as it is usually produced from animal products) or stimulate an immune response. No scaffold materials have ideal structures and properties that totally resemble natural extracellular matrix as natural ECM comprises of complex architecture made up of structural proteins (collagen and elastin), specialized proteins, and glycosaminoglycans. This architecture provides not only structural support for tissue but also a selective dynamic environment that is remodeled via biochemical signals to direct cellular responses.[84] A scaffold should combine the best properties of biomaterials and be as close to the physiological environment of the ECM as possible.[80]

Growth Factor as Regulator

Regulating molecules are required for SHED to generate endothelial cells, odontoblasts, and neurons that will form the dentin-pulp complex architecture.[71,85,86] They work in signal transduction pathways to regulate cell proliferation, migration, and differentiation into specific phenotypes. BMPs, PDGF, FGF, TGF, EGF, and IGFs are the most common WNT proteins.[87–89]

VEGF stimulates SHEDs to undergo endothelial cell differentiation. In an experiment described by Annibali (2014), SHED was incubated in endothelial cell growth medium (EGM-2MV). This medium contains ascorbic acid, hydrocortisone, rhEGF, FBS, R3-IGF-1, rhbFGF, rhVEGF, and VEGF.[71,85] MEK1/VEGF/ErK, Wnt/VEGF/-catenin, and Notch-EphrinB2/VEGF-DLL4 signaling pathways regulation in response to VEGF stimulation, the expression of VE-Cadherin (endothelial markers), VEGFR2, and CD31 increased dramatically.[71,85] Furthermore, the endothelial-like cells generated by SHED could anastomose with the host vascular network which is demonstrated by an experiment using LacZ tags and galactosidase staining.[85]

Odontoblast differentiation was observed after BMP-2 stimulation. This regulatory molecule involves in the production of tubular dentin, odontogenesis and morphogenesis. Dentin sialophosphoprotein (DSPP) marker will be abundantly expressed for this distinction.[85,90–92] The production of DSPP is also influenced by two catalytic subunit signaling complexes that target rapamycin complexes 1 and 2. (TORC 1 and 2). TORC1, which is also required for protein synthesis and translation, regulates and directs cell cycle, growth, and proliferation. Suppression of TORC1 prevented mineralized matrix deposition, which also severely limited synthesis of DSPP. TORC2 influences both cell survival and cytoskeleton rearrangement. Inhibition of TORC2 promoted mineralization.[85,93]

SHED culture in DMEM supplemented with vitamin D3, ascorbic 2-phosphate, dexamethasone, and glycerol phosphate resulted in odontoblast-specific genes DMP1 and DSPP expression. Culture also showed mineralized matrix as visualized using Alizarin red.[85,94]

Different techniques for isolating SHEDs revealed various traits for odontoblast differentiation. Despite having functioning odontoblasts phenotype, SHEDs isolated by direct outgrowth showed decreased rate of mineralization and abnormal cell elongation and polarization due to vertical orientation of the cell body alongside the dentin-like matrix. While SHEDs isolated using enzymatic dissociation formed fast mineralized tissue and kept spindle-shaped morphology.[85,90]

In immunocompromised mice, the ability of SHEDs to develop into odontoblasts was examined. The dorsum of subcutaneous tissue was implanted with ceramic tricalcium phosphate/hydroxyapatite (TCP/HA) powder and SHED combinations.[85]

This resulted in the formation of dentin-like structures. However, transplant cannot form a complete dentin-pulp-like complex. Only 25% of the clones from one of the colony-derived SHED strains transplanted were found to produce ectopic dentin.[85]

In another study, slices of extracted third molar teeth were used. To create a porous biodegradable scaffold, poly-L-lactic acid was used to fill the pulp chamber, which was in close contact with the predentin layer. After 1428 days, cells adjacent to the predentin exhibited an active dentin-secreting odontoblast. DSP was also expressed. Cell nuclear location is thought to be polarized eccentrically. Cell displayed cell-cell gap junctions, a well-developed rough endoplasmic reticulum, the golgi complex, and a large number of vesicles.[85]

SHED has also been confirmed to be able to develop into neurons. Several neuronal markers, including glutamic acid decarboxylase (GAD), III-tubulin, nestin, 2',3'-cyclic nucleotide-3'phosphodiesterase (CNPase), tyrosine-hydroxylase (TH), polysialylated-neural cell adhesion molecule (PSA-NCAM), glial fibrillary acidic protein (GFAP) were expressed by SHED derived neuron.10-12, Several cytokines include FGF8, SHH, bFGF, and GDNF influence SHED neuronal regeneration.[86,95,96]

FGF8 is responsible for the dorsalization of the anterior neural tube.[96] The notochord secrets SHH during development to induce a general ventral cell destiny in order to generate floor plate and motor neurons. bFGF acts as a proliferation and differentiation regulator. After five days of culture on poly-L-lysine coated dishes without serum, the cells rapidly lost their mesenchymal appearance and took on a more neuronal appearance, including neurite-like outgrowth. Continued injection of SHH/FGF8 generated neurons with developed and extended axon or dendrite like structures.[85,96]

Upregulation of lncRNA C21orf121 and the downregulation of miR140-5p aid in the differentiation of SHED into neuronal cells. lncRNA C21orf121 prevents BMP2 from binding to miR140-5p, that subsequently increases BMP2 production and promotes SHED neurogenesis.[86,97]

Dentin Pulp Regeneration

Dentin pulp regeneration aims to revitalize necrotic, infected, or lost pulp teeth by restoring the morphology and function of the pulp. Ideal pulp regeneration should possesses natural structures such as nerve fibers and blood vessels, allowing nutritional, defense, sensation, and immunological functions to be restored.[10,98] Growth factors, scaffolds, plasma, or other associated cells such as dentin/odontoblasts, fibroblasts, or endothelial cells may provide regenerative signals in this regeneration process resulted in cell migration, proliferation, differentiation, angiogenesis and extracellular matrix deposition.[28,99]

Endothelial cells differentiate into mesodermal precursor cells (angioblasts) during vasculogenesis, whereas new blood vessels are formed from previously existing blood vessels during angiogenesis. VEGF is the main regulator of angiogenesis and can also increase vascular permeability.[28,100] FGF, another growth factor with an angiogenic role, can attract DPSCs to migrate and proliferate.[28] PDGF can significantly boost cell proliferation, angiogenesis, and odontoblast differentiation.[101,102] BMP7 promotes the formation of dentin (dentinogenesis).[103]

Nerve Growth Factor (NGF) plays an important role in the nervous system growth, differentiation, and defense mechanisms by preventing apoptosis and reducing neuronal degradation. NGF expression is typically increased in damaged and developing teeth; this growth factor promotes the proliferation of sensory and sympathetic nerve cells.[28] NGF is also involved in the processes of angiogenesis by inducing VEGF upregulation. NGF binds to tyrosine kinase receptor (TrkA) on the cell surface, resulting in TrkA phosphorylation and activation of multiple signaling pathways, including PI3K/Akt, Ras/Raf/MEK/ERK 1/2, and PLC/PKC. Activation of each of these pathways result in a variety of biological functions, including the prevention of apoptosis.[104–106]

Conclusion

In responding to the challenges in dentistry to maintain pulp tissue and prevent tooth loss with irreversible or necrotic pulpitis, regenerative endodontics by utilizing tissue engineering technology can be developed. In this technology, the utilization of SHED which has excellent potential with high proliferation speed and ability to differentiate into various cell-forming dental pulp cells, collagen scaffold as a medium for cell growth and function, and growth factor as a regulator can be utilized to repair and regenerate pulp tissue by regenerates pulp tissue naturally and fully functional again.

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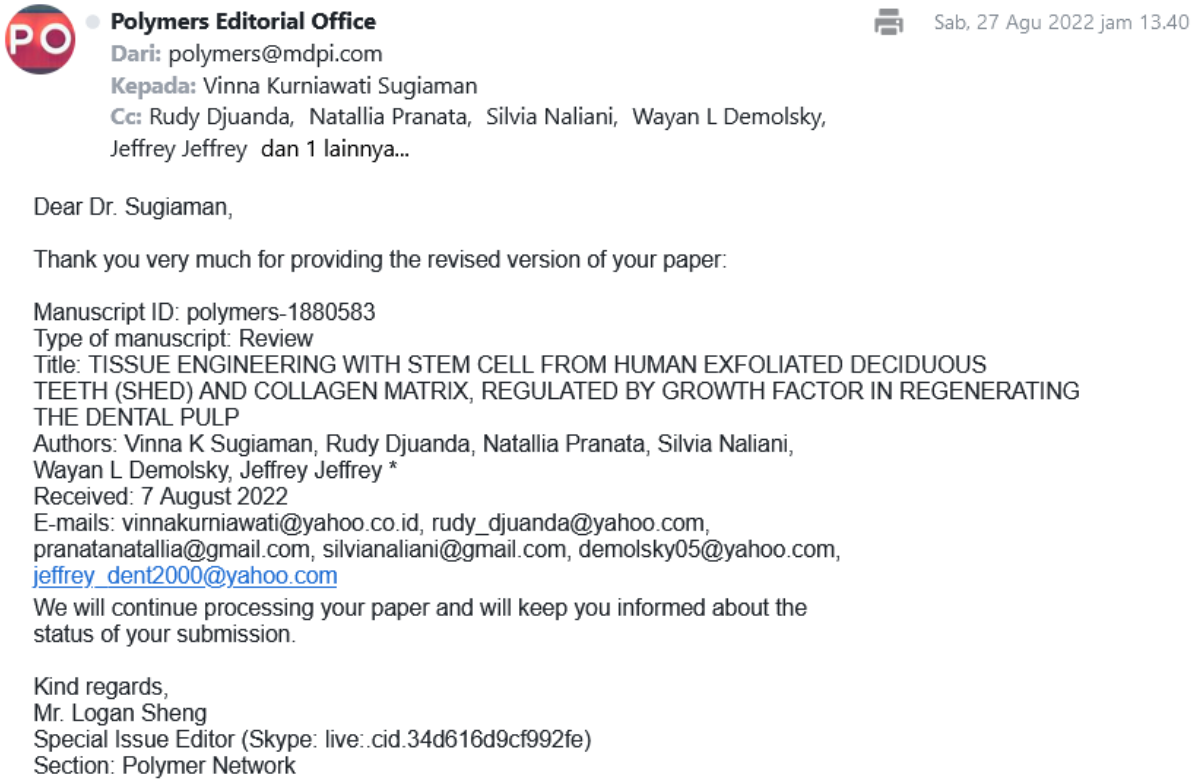

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