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The use of 3D printing and growth factor in cosmetics medicine

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Abstract. The equipment we have designed consists of two main parts: the outer part and the inner part. The outer part features a 3D printed nose bridge made from Polylactic acid (PLA) and collagen. This combination of materials serves a dual purpose: the PLA aids in replacing dead skin cells and supports blood clotting, which facilitates faster post-operative recovery. Meanwhile, the inner part is filled with autologous fat infused with connective tissue growth factor. This choice is grounded in the fact that cartilage, a key component in this context, belongs to the connective tissue category. Under optimal conditions, this innovative equipment demonstrates promising efficacy.

Keywords: Polylactic acid (PLA), autologous fat, connective tissue growth factor, augmentation rhinoplasty

1. Introduction

In the swiftly advancing landscape of cosmetic medicine, the widespread acceptance and growing willingness of people to embrace its services is evident. However, recent news highlights a concerning trend of accidents arising from improper treatments and substandard materials within the realm of cosmetic medicine. It is evident that while technologies like 3D printing and growth factors have demonstrated their effectiveness in addressing various medical conditions, their adoption within cosmetic medicine, particularly in procedures like rhinoplasty, remains limited.

This prompts an intriguing notion: the fusion of 3D printing technology with growth factors as a strategy to mitigate the risks associated with immune reactions. In the subsequent discussion, we delve into the mechanics of these technologies, their current applications, and elucidate why their integration holds promise as a novel approach within the domain of cosmetic medicine.

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2. 3D printing

2.1. Introduction

3D printing is a process that uses computer-aided design to create specialized objects which is full three dimensional printing creat objects layer by layer. The layers are extremely thin to between 16-180 microns. 3D printing has another name which is called additive manufacturing [1]. 3D printing was first invented by Charles Hull in the 1980s. The prototyping technology that he invented is stereolithography, the most commonly known 3d printing technique. No long after Charles Hull invented stereolithography, selective laser sintering was soon invented by Carl Deckard. Then, 3D printing started to became popular [2].

2.2. 3D printing techniques

2.2.1. Stereolithography (SLA). Stereolithography is one of the most commonly used technique of 3D printing, as shown in a figure 1. Stereolithography is to use an ultraviolet laser beam and focus on a surface of photosensitive thermoset polymers, which come in a liquid form, to induce polymerization of the liquid in that region and transform it into a polymerized solid [3].

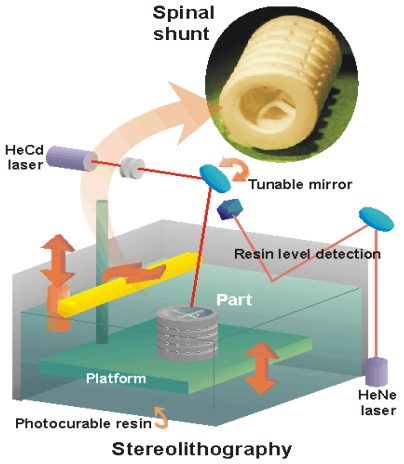

Figure 1. Work principle of stereolithography [4]

Even though it is a very old technique of 3D printing, it has many benefits. For example, it has a high precision due to the thinness of the layers applied in stereolithography. The thinness is between 0.05-0.10mm. Another benefit is the cost of stereolithography is relatively cheaper than other methods. However, the material that are most frequently used this technique is resin, which is a liquid polymer, so it causes the prototype more fragile [5].

Stereolithography is not suitable to print a scaffold for nose bridge bone. Even though it has the feature of high precision and cheap, most of the liquid polymers are fragile due to segmental relaxation [6]. This may cause higher risk of failing the operation and people need to be very careful before the nose bridge bone has completely grow into the scaffold.

2.2.2. Selective laser sintering (SLS). Selective laser sintering is a type of Power Bed Fusion (powder based), which is an additive manufacturing process that uses the energy provided by the laser to melt and fuse the powders and stack layer by layer to form a print of the 3D model, shown in figure 2. Selective laser sintering can be used in a variety of different applications. Automotive hardware prototypes, electronic hardware and medical and pharmaceutical equipment are some examples of the usage of selective laser sintering [7].

What makes selective laser sintering more prominent is that it can 3D print biocompatible materials such as nylon11. It also has a high strength as there is a very strong adhesion between layers.

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Additionally, SLS is the fastest addictive manufacturing process. The only drawback of this type of 3D printing is the SLS printed parts will have a porous surface, but the porous can be sealed by applying a coat such as cyanoacrylate [8].

Selective laser sintering is suitable for printing the scaffold of nose bridge bone. It has high strength and it can print biocompatible materials. This can prevent exclusion reactions and allergic reactions to the greatest extent. Strong scaffold also lowers the risk of fracturing. Even though it has a porous surface, which affects the beauty of the scaffold, the porous can be filled.

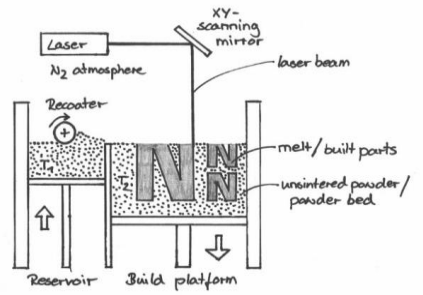

Figure 2. How does selective laser sintering (SLS) work [9]

2.2.3. Fused deposition modeling(FDM). Fused deposition modeling, also known as fused filament fabrication (FFF) is a modern and relatively advanced 3D printing technique invented only over 20 years ago. FDM becomes the second commonly used technique after SLA. Fused deposition modeling creates 3D structure by plastic filaments layer by layer through melt-extrusion, shown in figure 3. FDM is controlled by rapid prototype computer which produce parts made of porous material through the manufacturing method of layer by layer. The application of FDM is endless. This includes biomedicine, textiles, automotive, construction and aerospace [10].

Even though the printed model of have rough surfaces, the post-processing can help to achieve a smooth surface. Accurate prototyping and low costs make FDM a widely used manufacturing technique. Speed is also one of the biggest reasons to use FDM. In the field of dentistry, FDM was regarded as 'dental master models' as it can complete prototyping in only a few minutes or few hours. FDM technology also accept a wide range of materials. Polylactic acid, polyethylene terephthalate glycol and nylon are common filament material used in FDM. These are all biocompatible materials [11].

Fused deposition modeling is suitable for printing the scaffold of nose bridge bone. This type of technology basically meets the need of printing a biocompatible and biodegradable nose bridge bone. Faster speed can improve the efficiency. The feature of having a rough surface can be ignored. Unlike porous structure, rough surface will not form irregular shapes. The scaffold is also planned to be biodegradable, so it will disappear after the nose bridge bone grow.

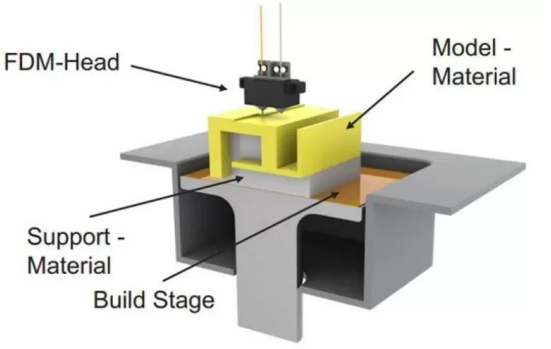

Figure 3. How does FDM work [12]

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2.3. 3D printing materials that can be used in cosmetic medicine

2.3.1. Polylactic acid (PLA). Polylactic acid($C_3H_4O_2$) is a biodegradable and recyclable polyester that produce through microorganisms. It decomposes to water, humus and carbon dioxide. PLA is produced by fermentation of sucrose or glucose and it has a high purity. There is a wide range of application of PLA such as engineering plastics, food packaging and textiles. PLA has a high stiffness and strength compared with other polyester in room temperature [13]. This is because PLA has a relatively low glass transition temperature, between 43℃ to 62℃, which means it not soften until the temperature reaches 43℃-62℃.

2.3.2. Polyurethane fiber (PU). Polyurethane fiber is a synthetic fiber also referred to as spandex as a genetic name. It is highly elastic as a rubber, but stronger than rubber. Polyurethane fiber is produced through a process called electrospinning princess. This technique includes stretching polymer fluid under strong electric fields into the fine filament. Polyurethane fiber always blend with other fibers, there are no product manufactured of 100% polyurethane fiber. Hence, the properties can change by combining hard and soft segments. This kind of fiber is called biocomponent fiber. PU is also biodegradable and biocompatible [14].

2.3.3. Collagen. Collagen is a very ideal material is cosmetic medicine made up of amino acids. It is a structural protein that can be found in every animal organism where it provides the fundamental structural support. This protein is mainly responsible for healthy joints and skin stretchiness in human body. Collagen have high resistance to stretching and rigidity. There are already practices injecting collagen into humming skin to improve the density and quality of the sin [15]. There are barely any exclusion reaction or allergic reactions happening after the injection of collagen. Collagen will biodegrade during the process of bone resorption. After collagen biodegrade, it will turn back to amino acids and travels into the bloodstream.

3. Recent research about growth factor

The groundbreaking discovery of growth factors by Stanley Cohen and Rita Levi-Montalcini in 1986 paved the way for their widespread use in medical treatments, where they demonstrate remarkable abilities in reducing bone loss [16] and promoting protein formation [17]. Extensive research on growth factors [18] uncovers several types of growth factors, including the Epidermal growth factor (EGF) family, Fibroblast growth factor (FGF) family, Transforming growth factor-ß (TGF-ß) family, Bone morphogenetic proteins (BMPs), Platelet-derived growth factor (PDGF), Vascular endothelial growth factor (VEGF), and Connective tissue growth factor (CTGF) [19]. The unique functions of these growth factors make them indispensable in medicine, as they actively promote growth and healing.

3.1. EDF family

The EGF family is a valuable resource in clinical care for treating patients with ovarian cancer. Comprising four structurally-related type one transmembrane tyrosine kinase receptors, these receptors form a complex with 89 cytosolic tyrosines, where 40 can interact with one or multiple adapter proteins. Upon phosphorylation, these receptors trigger downstream signaling pathways. The adapter proteins demonstrate varying binding sites when associating with an ErbB receptor and show different binding sites with various members of the ErbB receptor family, facilitating the activation of a complex network of signal transduction pathways. This has revealed numerous abnormal downstream signaling pathways around malignant ovarian tumors, highlighting the potential of the EGF family for clinical care in ovarian cancer treatment [20].

3.2. FGF family

Fibroblast growth factors (FGF) are instrumental in promoting the formation and functions of nervous system,shown in figure 4. The FGF family encompasses nine related polypeptides that activate

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mitogenic and cell survival processes extensively. Notably, Acidic FGF (FGF-1) and basic FGF (FGF-2) act as potent mitogens for various cell types, being the first two identified, sequenced, purified, and found to be widely expressed.

The FGF family also includes FGF-3, frequently be used to target the mammary tumor virus in mice, while FGF-4, 5, and 6 demonstrate activation of transform upon introduction to NIH 3T3 cells. Additionally, FGF-7 serves as a mitogen for keratinocytes, FGF-8 for mammary carcinoma cells, and FGF-9 for astrocytes.

Ranging from 155 to 268 amino acid residues, these nine FGFs share the same central region which is formed with 140 amino acids. FGF signaling transformation generally occurs through when transmembrane tyrosine kinase receptors are activated.

In mice, if FGFR1 or FGFR2 genes is destroyed, it may lead to the death of early embryonic, while FGFR3 break results in bone overgrowth. In humans, it is already known that point mutations of FGFR1, 2, and 3 is related to skeletal disorders [21].

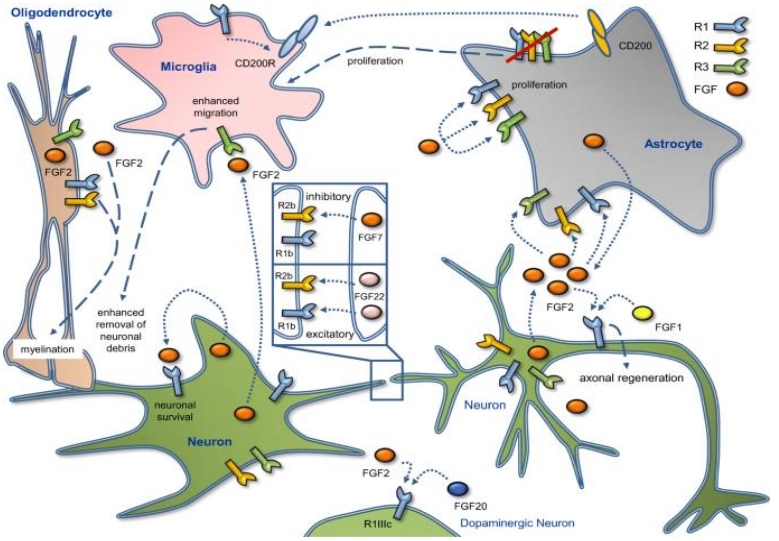

Figure 4. FGF signaling in the Diseased Nervous System [22]

3.3. TGF-ß family

TGF-ß (Transforming Growth Factor-ß) has compelling in vivo evidence of its antiproliferative action. It refers to dimeric products resulting from various genes, identified through protein isolation or cDNA cloning. Currently, researchers have distinguished five different types of TGF-ß.

Initially, TGF-ß was be regarded as the manifestation of activation produced by retrovirally-transformed cells. Among the TGF-ß types, TGF-ß1 abounds in human and porcine blood platelets, making it the richest source of this factor. In contrast, TGF-ß2 is found in human placenta, porcine platelets, and bovine bone, distinguished from TGF-ß1. The names CIF-A and CIF-B were previously used to denote both TGF-ß1 and TGF-ß2 due to their cartilage inducing activity.

Researchers have successfully cloned TGF-ß2 cDNAs from human, monkey, and mouse libraries, affirming their growth-inhibiting properties.TGF-ß3 in human body was initially be detected at the eDNA level and later expressed through recombinant methods.

In vivo experiments, inert polymer beads with TGF-ß1 impregnated, is implanted near the epithelial end buds of immature mammary glands and the result effectively demonstrated its antiproliferative action. Additionally, intravenous injection of TGF-ß1 or TGF-ß2 adversely impacts the proliferative response of liver regeneration in the body. Furthermore, TGF-ß plays a role in promoting cell withdrawal from the proliferative state, as observed in the epidermis after phorbol ester treatment, supporting the concept of TGF-ß inducing cell withdrawal. Nevertheless, it's important to note that TGF-ß can also stimulate cell proliferation, coexisting with other cellular responses [23].

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3.4. BMPs

BMPs (Bone Morphogenetic Proteins) play crucial roles in maintaining arthrosis integrity, initiating bone repair after fractures, and participating in blood vessel remodeling [24]. As a distinctive proteins group in the Transforming Growth Factor beta (TGF-ß) superfamily, BMPs were firstly discovered by Urist in 1965. Their ability to induce bone formation was demonstrated when applied to demineralized bone matrix in ectopic sites in rats [25].

Substantial evidence supports BMPs' role in inducing bone induction, repair, and maintenance, along with their significance in mammalian embryological development. During embryogenesis, BMPs are pivotal in regulating dorsal-ventral patterning and contribute significantly to processes such as cell apoptosis, neural cell differentiation, limb bud patterning, and epithelial-mesenchymal interactions, as described by Jones [26].

The TGF-ß superfamily comprises more than six members, including activins/inhibins, TGF-ß, GDFs (growth and differentiation factors), mullerian inhibiting substance, Drosophila dpp, Xenopus Vg1, and the else. BMPs significantly influence cell differentiation, growth inhibition, proliferation, and maturation arrest, and it depends on the microenvironment the cellular exist and the interaction of other regulatory factors [27].

3.5. Platelet derived growth factor (PDGF)

PDGF (Platelet-Derived Growth Factor), is utilized to prevent atherosclerotic lesions and enhance bone resorption. Its discovery dates back to 1974 when researchers identified platelets as the origin of mitotic figure activation in the whole serum, impacting serum-dependent cell growth.

Derived from human platelets, PDGF is a small cationic glycoprotein with a molecular weight about 30,000. Its mitogenic activity is influenced by disulfide bonds, leading to the formation of various protein species within the range of 14,000 to 17,000 Mr. These species consist of two related but distinct chains, known as chain A and B. While human platelet-derived PDGF forms a heterodimer of these chains, experiments with porcine PDGF reveal B-B homodimers, while osteosarcoma cells contain A-A homodimers, indicating mitogenic properties for both chain homodimers A and B [28].

Interacting with responsive cells, PDGF rapidly promotes phosphatidylinositol turnover, resulting in prostaglandin production, including PGl2 and PGE2. Elevated levels of PGI2 and PGE2 may boost bone resorption. These prostaglandins may inhibit vasodilatory and antiplatelet agents, playing a vital role in preventing atherosclerotic lesion formation [29]. The initial discharge of free arachidonic acid suggests the activation of phospholipase A2 or the start of phospholipase C-diglyceride lipase pathway. Incubating cells with PDGF combined with very low-density lipoprotein (VLDL) or low-density lipoprotein (LDL) significantly increases prostaglandin synthesis, implying LDL pathway involve in the process of prostaglandin metabolism when cells encounter some mitogens like PDGF [28,30].

3.6. Vascular endothelial growth factor (VEGF)

Vascular endothelial growth factor (VEGF) assumes a crucial part in the regulation process of blood vessel formation and tumor control. It acts as a highly specific mitogen, primarily affecting vascular endothelial cells [31]. Five distinct isoforms of VEGF are produced because of the alternative splicing from a single VEGF gene the five isoforms are vary in molecular mass and possessing unique biological properties. Among these properties, their ability of forming bonds with cell-surface heparan-sulfate proteoglycans are different. VEGF promotes both endothelial cell proliferation and migration, while also inhibiting apoptosis. In vivo, it induces blood vessel infiltration and formation, significantly contributing to the regulation of vasculogenesis.

Disruptions in VEGF expression can expedite tumor angiogenesis, thereby fostering solid tumor development. Consequently, targeting VEGF signaling may aid in the treatment of diverse tumors. VEGF interacts with two types of tyrosine-kinase receptors, VEGFR-1, and VEGFR-2, and the combined product predominantly expressed in endothelial cells [32].

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3.7. Connective growth factor

The discovery of Connective Tissue Growth Factor (CTGF) traces back to 1991 when Bradham et al. identified a polypeptide growth factor secreted by human endothelial cells. This factor stimulated DNA synthesis and chemotaxis in fibroblasts.

Simultaneously, researchers found fisp-12 or ßlG-M2, obtained from mice, is an early gene activated by blood serum or Transforming Growth Factor-ß (TGF-ß) from fibroblast cell lines in murine bodies. This finding coincided with the authentication of the cDNA test of human CTGF (hCTGF).

CTGF is one of the six new genes in CCN family, including cyr61, nov, elm1, cop1, and WISP-3. They are classified due to their structural similarities. Recent studies on the CCN family have intensified, revealing significant functional differences between the CCN family and CTGF [33].

4. The use of 3D printing and growth factor in rhinoplasty

The proposed equipment is designed with two distinct components: the outer and inner sections. The outer component comprises a 3D printed nose bridge bone, utilizing Polylactic acid and collagen as its foundational materials. Meanwhile, the inner component consists of autologous fat infused with connective tissue growth factor. In the following sections, we will provide individual explanations of the outer and inner structures, elucidating the reasons behind their potential for ideal performance.

Our core concept revolves around utilizing connective tissue growth factor to stimulate cartilage growth in the nasal region, effectively achieving the goals of rhinoplasty. To precisely regulate and enhance this growth process, we have incorporated 3D printed particles. These particles serve as a controlled platform to guide and optimize the growth dynamics, resulting in a harmonious and successful outcome.

4.1. The 3D printing part

The scaffold utilizes a combination of Polylactic acid and collagen as the core materials for the 3D printed nose bridge bone. In a deliberate effort to minimize exclusion reactions and allergic responses, the collagen used is sourced from the patient's own body. The chosen technology for this endeavor is fused deposition modeling. A specific variant of Polylactic acid, poly-l-lactic acid, demonstrates the remarkable ability to stimulate collagen synthesis [34]. Consequently, this property holds significant promise in fostering collagen production, thereby facilitating the replacement of dead skin cells and promoting efficient blood clotting. These unique attributes play a pivotal role in expediting the post-operative recovery process for the patient.

The structural configuration of the 3D printed nose bridge bone is depicted below, shown in figure 5. While its overarching form mimics that of a bridge, the precise contours are meticulously tailored to cater to the individual patient's requirements. The external surface of the model adopts a porous composition, with these pores being imbued with collagen. This non-uniform structure is deliberately chosen to ensure precise control over the collagen distribution, avoiding the pitfalls of excessive collagen application, which may not necessarily yield beneficial outcomes. Notably, both the inner and outer surfaces possess a deliberately rough texture, fostering a strong attachment between the scaffold and the nose. This essential feature prevents any undesirable shifting of the scaffold.

Within this bridge-like scaffold, a layer of growth factor is situated between the scaffold and the original nasal structure. Crucially, the scaffold begins its biodegradation process upon contact with the natural bone. The planned thickness of the scaffold ranges between 2.19mm and 2.23mm [35], closely approximating the average thickness of the human nasal bridge bone. It's important to note that this thickness may vary based on the gender of the patient, as male bones generally exhibit greater thickness compared to those of females.

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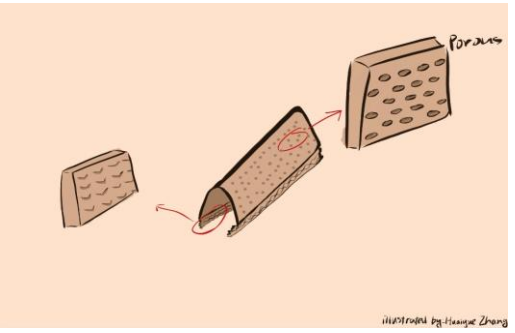

Figure 5. The preliminary sketch of 3D printing part

4.2. The growth factor part

The inner substance comprises autologous fat, sourced from the individual's own body and infused with connective tissue growth factor. The utilization of autologous fat as a replacement for conventional fillers in facial rejuvenation gained traction as early as 2007. The advantages of this approach over artificial fillers are apparent: autologous fat offers a softer and longer-lasting solution within the human body [36]. The presence of growth factors within the fat aids in promoting cartilage growth, effectively achieving the objective of a heightened nose bridge bone.

Traditionally, rhinoplasty involved using polymers as fillers to enhance the nose bridge bone. However, this method carried the inherent risk of rejection reactions, potentially leading to healing complications. Attempts to use rib grafts from the body were made, but rejection reactions persisted in some cases. The use of autologous fat reduces the likelihood of rejection reactions since the body already contains fat surrounding the nasal cartilage.

To stimulate cartilage growth, connective tissue growth factor is employed, given that cartilage belongs to the realm of connective tissue. Evidence demonstrates that connective tissue growth factor aids in the recovery of injured rat knee cartilage [37]. By extension, a similar positive outcome is anticipated in the human nasal context. Concerns about excessive cartilage growth and resultant disfigurement are alleviated by meticulously controlling the concentration of growth factors and the constraints of the 3D printed particles. This comprehensive control ensures predictable results. Furthermore, this novel approach eliminates concerns about filler migration, a concern often associated with traditional methods.

5. Conclusion

In the preceding text, we have already demonstrated the probability of augmentative rhinoplasty through the application of connective tissue growth factor along with 3D-printed particles composed of Polylactic Acid (PLA) and collagen. If this innovative approach were to be incorporated into cosmetic procedures, it holds the potential to significantly reduce the occurrence of adverse reactions, consequently minimizing accidents caused by rejection responses. Furthermore, this novel technique may yield superior outcomes compared to conventional treatments.

Acknowledgement

Zeyu Qi and Huaiyue Zhang contributed equally to this work and should be considered co-first authors.

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