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GENETIC ENGINEERING TECHNIQUE: AN EFFECTIVE APPROACH FOR WOUND INFECTION MANAGEMENT

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ABSTRACT: Infection is the major problems in a diabetic patient where the healing process are slow down and increases complications. Antiseptics helps to limit the growth of unwanted bacteria (opportunistic pathogen) superficially but do not work in case of deeper infection as its mode of action slows down after some time. The use of antibiotics also emerges multi-drug resistant pathogens, which are considered more dangerous and difficult to treat. Therefore, a new approach to wound therapy is expected that can escape many of the problems associated with current antibiotic treatments. In this regards, genetically engineered bacteria and their products may enhance the natural wound healing process. Wound healing factors like growth factors as well as fibroblast can be incorporated into bacteria genome which will promote healing mechanism speedily. In this aspect, modified bacteria will also prevent the unnecessary growth of the opportunistic pathogen. Many advantages are anticipated from the use of genetically modified organism and its products in wound treatment. The present review is focussed on the various approach of genetic engineering technique in effective wound healing and wound infection treatment.

Keywords: Genetic engineering, Wound healing, Multi-drug resistant, Antibiotics

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INTRODUCTION: Wounds occur when anything damages the dermis layer of the skin. Wounds can be opened or closed type. Opened type of wounds [1] are incisions, lacerations, abrasions, avulsions, puncture, penetration, and gunshot which are caused by an object [2]. Fewer wounds have been categorized as closed type such as hematomas and crush injury [3]. Based on the contamination level, wounds have been classified as clean, contaminated, infected, and colonized [4].

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Infection of wounds with harmful bacteria prevents the healing process and increases the risk of complications.

Wound Healing: Wound-healing (WH) is a series of preparation that undergoes in our body to repair a wound collectively known as wound healing process [5]. This process is thought to be a set of interdependent improvements that go through four overlapping sequential phases: a) hemostasis phase followed by b) inflammatory, c) proliferative and d) remodeling phase [6, 7]. It is observed that unhealed wounds for a longer duration have probability and incident of infection by harmful pathogens also rises. More than 15% of all patients with diabetes have been believed to suffer from diabetic foot ulcers (DFUs), among which 84% undergo lower leg amputation [8].

Many studies have shown that wound infections persist untreated due to impair antimicrobial therapy that emerges resistant bacterial strains 9. Currently, there is no satisfying treatment for rapid healing of wounds.

Factor Affecting WH:

A) Local Factors:

Oxygenation: Oxygen is an essential factor for all cells during metabolic reactions. Oxygen consumption increases especially at the site of the wound due to high metabolic activity, oxidative killing and removal of foreign particles through phagocytosis, angiogenesis, re-epithelialization, keratinocyte formation, and differentiation, fibroblast proliferation, collagen synthesis, and wound contraction. Few studies claim that low oxygen tension due to vascular disruption has also been observed to stimulate the production and release of few cytokines and growth factors like PDGF, TGF-β, VEGF, tumor necrosis factor-α (TNF-α) and endothelin-1from macrophages, keratinocytes, and fibroblasts which assists in effective wound healing. In similar studies, it has been shown that hyperoxia increases ROS production, such as hydrogen peroxide (H_2O_2) and superoxide (O^2). This causes additional tissue damage. It suggests that appropriate oxygen level is essential in cell proliferation, migration, chemotaxis, and angiogenesis for ideal wound healing.

Infection: Usually, sterile wound repair faster than wounds with infections. Wound infections have been detected very common, critical, and problematic in hyperglycemia as well as immuno-compromised patient [10]. High blood sugar supports the growth of opportunistic pathogens at the site of wounds. Most of wounds (~98%) are contaminated by opportunistic pathogens [11]. In a retrospective study, a high predominance of aerobic bacteria was isolated from 614 individuals. The pathogens were identified as *S. aureus* (28.2%), *P. aeruginosa* (25.2%), *E. coli* (7.8%), *S. epidermidis* (7.1%) and *E. faecalis* (5.6%) [12]. These pathogens usually cause serious illness and life-threatening conditions. Polymicrobial infections, especially caused by *S. aureus* in combination with *P. aeruginosa* have also been documented [13]. 74.2% of *S. aureus* isolates from wound infection have shown Methicillin resistance [14]. In a similar study, *E. coli* has been reported as a chief uropathogen in diabetes patients followed by *Proteus* spps, *S. aureus*, *P. aeruginosa*, *Klebsialla* spps, and *C. albicans* [15, 16].

B) Systematic Factors:

Age: People above 60 years age are greater in number as per WHO. These groups are at high risk for impaired WH. The most predictable reasons for slow WH are an altered inflammatory response due to delayed T-cell infiltration, slow chemokine production, and reduce macrophage phagocytic capacity [17].

Studies in aged group mice have been claimed the delay in WH due to sluggish re-epithelialization, collagen synthesis, and angiogenesis compared to young mice [18]. Each phase of WH experiences impaired platelet aggregation, inflammatory mediator secretion, macrophages and lymphocytes infiltration, macrophage function, growth factors secretion, re-epithelialization, angiogenesis, collagen deposition, collagen turnover, remodeling and wound strength. In another study, older adults and aged mice showed improvement in WH after exercise. The improved healing response may be due to an exercise-induced anti-inflammatory response in the wound.

Hormones: Research studies suggest that sex hormones play an important role in WH through evidence of wound impairment in aged males than female. The sex hormones include estrogen, testosterone, dihydrotestosterone, and their steroid precursor dehydroepiandrosterone. Estrogen affects wound healing by regulating a variety of genes associated with regeneration, matrix production, protease inhibition, epidermal function, and inflammation.

This postulate that estrogen can recover age-related healing impairment in both men and women on the other hand, androgens control cutaneous wound healing unfavourably [19].

Diabetes Mellitus (DM): Investigations of wounds in various patients suggest that uncontrolled hyperglycaemic patients have a defect in WH mechanism compared to normal glycemic patient [20]. The factors that impair healing mechanism in diabetes involves high blood sugar level, glycated protein formation, free-radicals accumulation,

atherosclerosis, hypoxia, fibroblast dysfunction, obstructed angiogenesis, delayed neovascularization, and exhausted immune cells. Similarly, those undergoing major or minor surgery have been found an increased risk of infection compared to non-diabetics [21,] which is one of the major cause of morbidity and mortality in diabetic patients. In this regard, intentional glycemic control has significantly shown a decrease in infection frequency in DM [22]. Therefore, it has been suggested to regulate the high blood sugar in a diabetic patient before undergoing the surgical process. Children with Type I DM have found a significantly high level of HbA1c and increased risk for skin and soft tissue infections [23].

Obesity: Like diabetics, obese patients have also been reported at higher risk of post-cesarean infections [24]. Therefore, it is suggested that a patient should lose weight before undergoing any surgical operation to avoid unwanted complications and provide easy in treatment and management process.

C) Other Factors:

Nutrient: Nutrition is one of the major factors that contribute to proper WH. Habits of taking imbalanced diet lead to a shortage of many growth factors that are essential in WH mechanism [25].

Stress: Chronic diseases like cardiovascular disease, cancer, and type II diabetes mellitus are indirectly linked with stress. Stress is generally common in developing as well as under developing country which imparts great influence on human health and social behavior. Disturbance of body equilibrium has been recorded parallel with stress [26]. Stress leads to an increase in glucocorticoids and a decrease in pro-inflammatory cytokines level such as interleukins and tissue necrosis factors at the wound site.

Glucocorticoids act as an anti-inflammatory mediator which affect immune cells by inhibiting differentiation and proliferation, gene transcription, expression of cell adhesion molecules, and modifies cell-mediated immune responses [27]. These are essential in WH, but stress reduces their manifestation. Investigation in human and animals revealed a significant delay in WH due to psychological stress. Persons with Alzheimer or academic stress has proven delayed wound healing. Stress is an adverse emotional state that leads to anxiety and depressions which affect the physiological and behavioral health of a person. This results in strange practices like poor sleep, inadequate nutrition, less exercise, over-consumption of alcohol, cigarettes, and drugs. All of these factors play a negative role in WH [28].

Environment:

Occupation: WH may also be affected by the type of occupations that differs involvements of physical activities, hygienic environment, climates, timing and duration, and many other factors.

Hygiene: Individual immune system depends on the type of living style a person lives. Implementation of more hygienic living style may affect individual immunity by making more susceptible to general infections while people living with casual hygienic style are comparatively stronger in immunity [29].

Climate: It has been understood that the rate of metabolic activities in the human body varies with the type of climates (winter or summer) in which a person exists. Type of wound infection also depends on favourable climatic conditions. Some microorganisms are more active in less temperature here as others show optimal growth in high temperature [29].

Socioeconomic: Poverty: economic support is essential for full filling the basic requirements of any person. One of the major cause of malnutrition and undergrowth is poverty [30]. Treatment of any type of wound requires financial support so that greater care can be done. Wound treatment has to be compromised with an insufficient fund, which usually prolongs the WH [31].

Approach to Wound Management: Designing of therapeutic agents or stimuli to promote rapid wound closure is one of the most demanding attitudes by suffering patient.

Various advancement in molecular biology and health sciences has the enlightened researcher to understand the pathophysiology behind WH and insisted them to design new approaches to stimulate rapid WH in the patient.

Curcumin: It has been investigated in a diabetic induced rat model that curcumin has a vital role in wound healing mechanism. It has shown rapid wound closure through enhancement in fibroblast proliferation, collagen formation, and early epithelial layer regeneration [32].

Stem Cell: Monitoring of diabetic wounds, especially foot ulcers using stem cells, is thought to be new hope for effective treatment process which can reduce the chance of amputations [33].

Autologous Platelet-rich Plasma: Human subjects with chronic foot ulcers when treated with autologous platelet-rich plasma (PRP) have shown significant improvement in wound healing. Various growth factors, coagulation factors, and platelets present in PRP have been responsible for the progressive wound healing in chronic foot ulcers [34].

Collagen-Scaffold Membranes: Application of collagen nanofibre loaded with glucophage along with scaffold membrane containing poly-d-llactide-glycolide (PLGA) has shown improved wound healing in diabetic wounds. It has been suggested to increase collagen content during wound healing phase [35].

Galectin-1: In streptozotocin-induced diabetic mice model, it has been observed immediate healing of wounds after injection with galectin-1. It has been **suggested** that galectin-1 promote WH by regulating the production of reactive oxygen species in myofibroblast [36].

Fibroblast Growth Factor-2: an Animal model study using fibroblast growth factor (type 2) revealed that it has good potential for treating severe wounds through rapid angiogenesis, cellular proliferation, and connective tissue formation [37].

Xanthine Dehydrogenase siRNA: It has been suggested that uncontrolled and unmanaged hyperglycemia increases the production of free radicals in the form of ROS by overexpression of xanthine oxidase gene. Administration of xanthine dehydrogenase siRNA has shown improvement in wound healing by reducing the production of ROS through xanthine oxidase gene targeted inhibition [38].

Protein Tyrosine Phosphatase 1B Inhibitors: This suggests that the use of effective inhibitors against protein tyrosine phosphatase 1B can improve diabetic wound healing. This enzyme generally interferes with binding of endothelial growth factor to its receptors, which ultimately slows down WH [39].

Cytokines: In a diabetic animal study, it has been found that impair the production of few cytokines and growth factors leads to abnormal WH [40].

Proinsulin C-peptide: In a research experiment with streptozotocin-induced diabetic mice have been shown delayed in WH process in comparison to normal mice the but the use of C peptide has shown an increase in the rate of WH by inducing angiogenesis [41].

Skin-Derived Precursor Cells: In diabetic mice model, the therapeutic effect of skin-derived precursor cells has shown in early WH through accelerated vasculogenesis [42].

Heat Shock Proteins: Inadequate and impaired production of heat shock proteins has been suggested to be a leading cause of diabetic foot ulcers. These proteins support WH by fibroblasts recruitment to the injury site [43].

Immunization: Immunization with anti-pneumococcal and influenza vaccines has been recommended to reduce hospitalizations, deaths, and medical expenses [44].

Implementation of Genetic Engineering Techniques in Rapid Wound Healing: This review is focused on genetic engineering techniques (GET), which is supposed to bring innovativeness in the therapeutic process. In this regard, GET may help in producing modified bacteria with the enriched healing property; host defense peptides (HDP) and bioengineered skin substitute (BSS) as remedies for effective WH.

Suggested GE Strategies:

Fibroblast Growth Factor: Fibroblast growth factor (FGF) promotes proliferation & differentiation of endothelial cells, smooth muscle cells, and fibroblasts [45, 46]. FGF-1 and FGF-2 are most important fibroblast growth factors (FGF) that help in wound healing [47]. They stimulate a variety of cellular functions by binding to cell surface FGF-receptors in the presence of heparin

proteoglycans that give rise to angiogenesis and developing granulation tissue through the proliferation of fibroblasts and endothelial cells; both increase blood supply and fill up a wound space/cavity early in the wound-healing process. The FGF-receptor becomes activated through autophosphorylation induced by a mechanism of FGF-mediated receptor dimerization.

Receptor activation gives rise to a signal transduction cascade that leads to gene activation and diverse biological responses, including cell differentiation, proliferation, and matrix dissolution, thus initiating a process of mitogenic activity critical for the growth of endothelial cells, fibroblasts, and smooth muscle cells. FGF-1 is a potent mitogen for the diverse cell types needed to mount an angiogenic response in damaged (hypoxic) tissues. FGF-1 stimulates the proliferation and differentiation of all cell types necessary for building an arterial vessel, including endothelial cells and smooth muscle cells.

Use of pro-angiogenic growth factors such as vascular endothelial growth factor (VEGF) primarily drives the formation of new capillaries. Human clinical trials have been completed with FGF-1, in which the angiogenic protein was injected directly into the damaged heart muscle. An additional human trial using FGF-1 has been completed to promote wound healing in diabetics with chronic wounds. FGF-2 helps in the promotion of endothelial cell proliferation and physical organization of endothelial cells into tube-like structures, thus promoting angiogenesis.

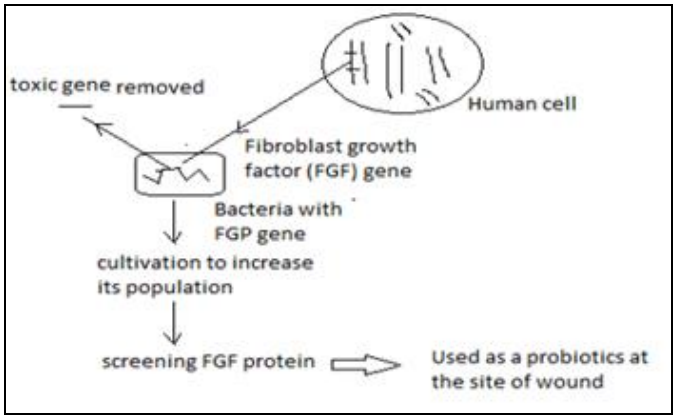

FIG. 1: PROPOSED MODEL FOR RAPID WOUND HEALING

FGF Production using GE Technique: Construction and amplification of FGF gene cDNA [48], selection of non-pathogenic bacterial strain, the transformation of selected bacteria with cDNA of FGF gene [42], identification and cultivation of transformed bacteria and wound healing study in an animal model using transformed bacteria and its product. Bacteria Selection strategies: Non-pathogenic(example skin normal flora) [49], Autolytic [50], carrying antibacterial characteristics [51], non-conjugating property, one that can be easily targeted with commonly used antibiotics and can grow in the wound environment.

Expected GE Outcomes: Rapid healing of wound, GE bacteria may grow at the wound site without harming and disturbing the healing mechanism, reduce the chance of pathogenic bacterial growth which is most commonly seen in the case of diabetic patient, reduce frequency of use of antiseptics to limit resistant strain formation against commonly used antiseptics and antibiotics.

Antimicrobial Peptides: Antimicrobial peptides are ubiquitous proteins that are part of the innate immune system and have been successfully found active against such antibiotic-resistant micro-organisms [52].

In this aspect, it has been demonstrated the feasibility of effective protein delivery via the micro-vascular system for unmanageable infections conditions. HDPs have shown innate immune modulators properties acting against a broad spectrum wound pathogens. Administrations of HDPs or induced expression of its gene or cutaneous gene therapy have emerged as potential treatment strategies for infected wounds [53].

Bioengineered Skin Substitute: BSS has been created for new therapeutic options that can act as an anti-infective living human skin tissue by providing an enhanced expression of the endogenous HDPs and cathelicidin to reduce infection and improve wound healing [54].

In this approach, clinically tested NIKS progenitor cells had been formed for generating a BSS exhibiting antimicrobial properties to provide a source of genetically uniform, nontumorigenic, and pathogen-free human keratinocytes. Enhanced expression of cathelicidin in a genetically engineered human BSS (bioengineered skin substitute) has been shown to inhibit the bacterial

growth of a multidrug-resistant clinical strain of *A. baumannii in-vivo*, creating a new and innovative therapeutic option for combating these debilitating wound infections while also promoting healing [55, 56].

DISCUSSION: Infection delays the healing process in the majority of the wound. This problem becomes more critical if the patient is diabetic. The poor condition of the patient can be seen these days at the trauma center. This touches the soul of any researcher and insists them to study, develop, and provide more effective treatment methods. Antiseptics are used to inhibit the growth of opportunistic pathogens, but its affectivity slows down slowly. Therapeutic use of antibiotics emerges multidrug-resistant pathogens [57]. This raises serious situations and is considered the difficulty in wound treatment and produce an unnecessary economic burden on suffering patient. The whole world is facing this problem.

Therefore, an urgent need is required for a new wound therapy method that can evade many of the problems associated with current antibiotic treatments. Genetically engineered bacteria are mostly used by many researchers for various benefits. This approach can also be applied for efficient wound healing and management. Wound healing factors like growth factors as well as fibroblast can be incorporated into bacteria which will promote healing mechanism speedily. Modified bacteria will also prevent the unnecessary growth of the opportunistic pathogen. Genetic engineering products specifically show the action at the target site. Many advantageous are expected from the use of genetically modified organisms and their product in wound treatment.

The present review is focussed on the various approach of genetic engineering technique in effective wound healing and wound infection treatment. Wound infections treatment process has become more problematic in some patients, especially those who are infant, old, diabetic, and immunocompromised. Various studies have shown the specificity and affectivity of GE methods in the successful treatment of diseases. BSS, antimicrobial peptides and growth factors like FGF have shown promising manner for the treatment of wound infections. In the future, the miracles of GE will be more employed to produce specific factors required for rapid wound healing. The world has awakened to realize today about the boundless opportunities for a genetic engineer in the field of medicine, diagnostics, and cures in the future. Genetic engineering tools have been found useful in numerous fields including medicine, research, industrial biotechnology and agriculture which has promised a huge scope for genetic engineers in India as well as abroad but its procedure has been considered as serious challenges to the environment, agriculture, animal and human health due to unique ethical and social concerns [59].

It seems to have many pros and cons of GE in which vaccines, therapeutic drugs and synthetic hormones like human insulin has been produced for the treatment of many diseases whereas many researchers has done objection on its use for many reasons such as it disturb the balance of biodiversity in nature, has negative impacts on the natural ecosystem and misuse of this technology due to production of biological warfare or weapons [59, 60, 61].

CONCLUSION: Through genetic engineering approach, several different wound healing factors can be synthesized through bacterial cell engineering strategies to reduce wound healing times. In this aspect, only a few studies have been assessed. Therefore, an approach of GE is thought to be needed for the effective therapeutic process through faster and effective wound healing approach. Further research is required to provide definitive evidence of efficacy.

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