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Review Article

Regenerative Medicine with Recombinant Human Granulocyte-Colony Stimulating Factor: Insights and Applications

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ABSTRACT

Regenerative medicine is an interdisciplinary approach which introduces treatment modalities that mimic natural biological mechanisms. These treatment modalities include growth factors, cytokines modulation of the signaling cascade, and customized tissue engineering therapies with the least invasive methods. Granulocyte colony-stimulating factor (G-CSF) is a hematopoietic cytokine that enhances granulocyte lineage cell proliferation, differentiation, and activation. Evidence-based studies have analyzed the effect of using recombinant human rh G-CSF on stem cell and progenitor cell recruitment and tissue repair and regeneration via anabolic protein upregulation and antiapoptotic mechanism enhancement. Promising regenerative effects of rh G-CSF administration have been reported in medical fields, such as providing long-term effects of neuroprotection in Parkinson's, Huntington's, and Alzheimer's diseases, ischemic disease, wound healing, diabetic foot repair, cardiovascular disease, reproductive biology, liver disease, and osteoid tissue regeneration.

Introduction

The regenerative field integrates numerous technological approaches and replacement modalities accomplished by multiple strategies involving surgery and prosthetic devices, including hip replacements and adjuvant biomaterial scaffolds. Organ and bone marrow transplants also play significant roles in regenerative medicine [1]. However, these treatments could lead to side effects that prevent patients from being considered in a "natural health" state post-treatment. For instance, organ transplant recipients often require immunosuppressive drugs, metal hip replacements might loosen over time, biomaterial scaffolding for tissue growth could induce inflammation, and bone marrow sources could vary in quality and might be contaminated during cell extraction procedures [2].

Regenerative medicine primarily depends on human cells, such as somatic cells, adult and embryonic stem cells, and those obtained from sources like the placenta, adipose tissue, and urine. Contemporary regenerative techniques incorporate a blend of cutting-edge technologies, advancing beyond conventional transplantation and tissue replacement [3]. These methods include molecular therapies, transplantation or activation of stem cells, tissue engineering, and preparing the human body to maximize safety and effectiveness. Such innovations aim to improve therapeutic outcomes and accelerate the transition of regenerative therapies into clinical practice, offering promising advancements [4,5].

Host environment modulation in the regenerative medicine approach

For any regeneration strategy to support function and tissue architecture effectively, it must achieve a harmonious integration in host innervation, vascularization, and the immune system [5]. Vasculature development during angiogenesis is facilitated by key angiogenic growth factors, such as vascular endothelial growth factor (VEGF), angiopoietin (Ang), platelet-derived growth factor (PDGF), and basic fibroblast growth factor (bFGF). Enhancing the host's regenerative potential by modulating its environment, whether through the administration of growth factor proteins or allogenic molecules, could trigger therapeutic responses indirectly [6]. This approach might involve activating a cascade of additional growth factors, followed by anabolic interactions with the host's target cells. These therapeutic protein analogs present notable advantages for pharmaceutical development. Protein products have a lower risk of toxicity and facility regarding route of administration and risk-benefit effect, and they could be more cost-effective to formulate and manufacture [7]. Thus, therapeutic strategies, such as growth factors and /or pluripotent stem cell induction, are among the blockbuster products of biotechnology [8].

Granulocyte-colony stimulating factor

G-CSF is a polypeptide glycoprotein produced by fibroblasts, bone marrow cells, connective tissue cells, macrophages, endometrial cells, and natural killer (NK) cells. It targets neutrophil precursors and mature neutrophils [9]. In its natural state, G-CSF has a three-dimensional structure. Its protein is made up of four helices that are linked together by amino acid loops [10]. G-CSF was initially cloned and first isolated from mice in 1983, followed by successful isolation outside the human body in 1986 [11]. rhG-CSF from a 175 amino acid sequence with two disulfide bonds has a molecular weight of 18,798.88 and molecular formula C845H1339N223O243S9 [12]. It is structurally different from the original G-CSF in terms of the total number of amino acids (presence of methionine at the "0" site) and the absence of a glycoside chain [13]. The control of neutrophil induction and proliferation is the main function of G-CSF in a healthy person. In addition, it has a role in regulating granulopoiesis via increasing granulocyte lineage cell proliferation and differentiation activation by interacting with its receptor located on the cell membrane [14]. There has been mounting interest in utilizing rhG-CSF to mobilize CD34+ hematopoietic stem cells from the stem cell-generating cells into the bloodstream.

Peripheral blood stem cells (PBSC) for use in hematopoietic transplantation in place of bone marrow [15], rh G-CSF, a genetically engineered drug, was granted endorsement from the US Food and Drug Administration (FDA) in 1991, which could be used in numerous aspects [16]:

- Treat severe congenital neutropenia [17].
- Used with patients receiving myelosuppressive anticancer medications to decrease the risk of infection (as manifested by febrile neutropenia).
- Enhancement of hematopoietic recovery after bone marrow transplantation [18].
- In healthy donors, rh G-CSF facilitates the growth, maturation, and survival of hematopoietic cells by regulating the expression of stromal-derived factor-1 (SDF-1) in bone marrow [19].

An average-sized adult generates approximately 120 billion granulocytes daily to replace the regular losses and support the regeneration of circulating neutrophils 20.

The production capacity of G-CSF may be amplified by at least 10-fold during strain environments such as injury or pathogen exposure to regulate the neutrophil response to inflammatory stimuli with effective anti-inflammatory properties [21]. As mentioned, the G-CSF is the fundamental influencer of neutrophilic granulocyte production regulation. This biological process establishes the framework for host defense systems [22]. Also, rh G-CSF has been found to enhance the availability of circulating hematopoietic stem cells to the heart, brain, and osteoid tissue as well as their capacity for mobilization and proliferation and promote the differentiation of mesenchymal stem cells derived from marrow to stimulate vascularization, innervation and to boost the anti-inflammatory properties [23].

Biological role of G-CSF

The G-CSF is a well-known hematopoietic cytokine, and G-CSF's biological effects are not confined to hematopoietic tissues; it has a wide variety of immunomodulatory functions, including the ability to enhance migratory activity, survival, and regeneration of many cellular elements in a dose-dependent manner [24]. G-CSF promotes the production of interleukin-10 by CD4+ and CD25+ regulatory T cells, which is utilized in higher macro-organism tolerance of the graft. Thus, the immunological tolerance is linked to the level of IL-10 production by T cells [25]. Recently, more evidence of rh G-CSF's immunoregulatory influence, particularly its effects on T cell function, has been obtained [21] (Figure 1).

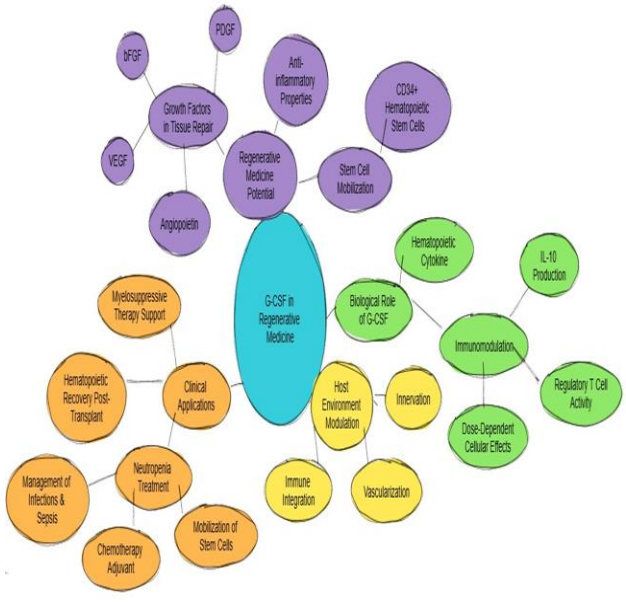

Figure 1: Overview of granulocyte-colony stimulating factor (G-CSF) in regenerative medicine. The diagram highlights the essential roles and applications of G-CSF, emphasizing its contributions to the host environment modulation through vascularization, immune integration, and innervation.

Roles of rh G-CSF in clinical practice

1- Treatment of neutropenia

The guidelines protocol of clinical practice recommends using rh G-CSF before hematopoietic stem cell transplants as a therapeutic approach to mobilize peripheral blood progenitor cells from healthy donors [26]. It is used in boosting the neutrophil recovery after consolidation chemotherapy in peripheral stem cell/bone marrow transplants in patients undergoing myelosuppressive chemotherapy for solid tumors and blood cancers, and myelogenous leukemia [27], and management of neutropenia caused by various diseases such as genetic disorders or immune deficiency syndrome [28]. The rh G-CSF could also be used as an adjuvant therapy, like in the case of neutropenia linked with medication-induced agranulocytosis, neonatal bacterial sepsis, pneumonia, infection, and burns [29].

2- Treatment of cardiac diseases

Recently, the rh G-CSF has been investigated to induce stem cells into the peripheral bloodstream to see if it could help with stroke [30], myocardial infarction, and congestive heart failure by either mobilizing the stem cells or its effect on reducing cells' apoptotic rate, improving mitochondrial function, angiogenesis enhancement, and fibrosis mechanism regulation [31].

3- Neuroprotective role of rh G-CSF

In neurology, the rh G-CSF has been utilized as a neuroprotective factor because of its unique properties, including anti-inflammatory effects, antioxidant and anti-apoptotic properties [32]. Long-term neuroprotective properties of the rh G-CSF have been shown in Alzheimer's, Parkinson's, and Huntington's diseases by suppressing brain shrinkage, initiating somatic growth, and strengthening neurocognitive processes such as short-term memory, motor functions, reflexes, and muscle strength [33].

4- Immunomodulation role of rh G-CSF

After myelosuppressive chemotherapy, when rh G-CSF is injected in combination with epithelial growth factor, it will regulate hematopoietic stem cell regeneration and proliferation [34]. In addition, to avoid febrile neutropenia (FN) events in patients with cell lung cancer, non-Hodgkin lymphoma, or breast cancer, the rh G-CSF as prophylaxis is regarded as a cost-effective modality for receiving therapy for patients who were at risk for FN [35].

Another regenerative property was reported in a meta-analysis by Qiu and colleagues in 2023, which proposes that rh G-CSF treatment has the potential for acute-on-chronic liver failure therapy, with significant improvements in liver function and survival rates [36].

5- Role of rh G-CSF in reproductive medicine

In the last several years, many meta-analyses and in-depth reviews have reported that rh G-CSF contributes significantly to successful pregnancy and decreases the abortion and infertile rate; this could be a viable option for women facing infertility who are undergoing in vivo fertilization (IVF) and experiencing thin endometrium or recurrent implantation failure [37-42]. Meng and colleagues studied the effect of intrauterine rhG-CSF infusion on the successful rate of pregnancy outcomes in patients with repeated implantation failure. The implantation success rate (28.44% vs. 12.44%, p = 0.012) and clinical pregnancy rate (48.95% vs. 27.35%, p = 0.011) in the rhG-CSF group were significantly higher than those in the control group [43].

6- Role of rh G-CSF in osteoid tissue healing

Regarding skeletal tissue repair, upon completing five consecutive doses of rh G-CSF, there was a substantial rise in CD34+ bloodstream cells [18], which could be distinguished into osteogenic, including vasculogenic, lineages [44]. Froberg et al. suggested that rh G-CSF stimulates osteoblastic activity via its ability to elevate bone formation indicators such as osteocalcin, bone-specific alkaline phosphatase enzyme, and transforming growth factor (TGFβ1), which has a positive effect on fracture healing [45]. Furthermore, rh G-CSF, when administered parenterally, neutralizes the negative consequences of non-steroidal anti-inflammatory drugs on bone repair. Moreover, the synergy between rhG-CSF and stem cell factor significantly improved osteoblast activity. It promoted local blood vessel formation, facilitating the regeneration of necrotic bone tissue and enhancing bone mechanical strength [46.47]. The mesenchymal stem cells activated by rhG-CSF led to elevated mRNA expression of bone morphogenetic protein (BMP2), a key regulator in bone formation and healing [48]. Several studies have explored the impact of administering rhG-CSF via injection on fracture healing in animal models [18], demonstrating that rhG-CSF enhanced bone healing in rats. However, the dosages in these experiments were 2.5 to 5 times higher than the standard dose recommended for human clinical use in healthy individuals [18]. Previous research has also highlighted that rhG-CSF administration significantly enhanced the healing of femur fractures, suggesting its potential application in human clinical procedures, such as planned osteotomies and fracture treatment [49,50]. In distraction osteogenesis experiments using a rat model, it has been indicated that the rh G-CSF administration speeds up the bone-healing process and regulates the release of progenitor cells [51]. Furthermore, Looi et al stated that the administration of rh G-CSF, besides inducing hematopoiesis, promotes fracture healing as well as non-union bone defects [52]. Since the rh G- CSF primarily targets neutrophil precursors and mature neutrophils [9], it also could enhance bone formation in an indirect mechanism by the role of neutrophil, as proved that the interaction between neutrophil and bone mesenchymal stem cells, leveraging innate and adaptive immune mechanisms could lead to the design of pioneering biomaterials that boost self-driven bone repair [53]. Additionally, the neutrophil cells which are stimulated by rh G-CSF injection have shown pro-angiogenic characteristics, this particular group of angiogenic neutrophils secretes matrix metalloproteinase-9 into the extracellular matrix to release pro-angiogenic growth factors, VEGF and FGF-2 into the extracellular matrix, which promote angiogenesis and in turn enhance bone regeneration [54]. All previous evidence-based studies reported the significant anabolic efficacy of rh G-CSF in enhancing osteoid tissue regeneration.

Bidirectional effect of rh G-CSF

The rh G-CSF has a bidirectional effect on osteoclast in a dose-dependent manner. Walsh and Choi stated that in a low dose of rh G-CSF, activated cells of the adaptive immune system, B lymphocytes, which are responsible for producing approximately more than half of the bone marrow-derived osteoprotegerin, which in turn inhibits osteoclast differentiation. In contrast, in heavy dose rh G-CSF; B lymphocytes activating osteoclast formation and enhance bone

resorption [55]. Furthermore, Oshitani and coworkers reported that injection of a heavy dose of rh G-CSF (250 µg/kg/day) intraperitoneally every 12 hours for 4 days before tooth extraction in a rat model might delay socket bone healing post-extraction by affecting bone metabolism, specifically through the inhibition of osteoblast activity and the increase of osteoclast activity [56].

Side effects of rh G-CSF

Typically, the rhG-CSF is widely accepted and safe in healthy people. Daily safe doses are 5-10 µg/kg [57]. Bone discomfort, fatigue, headach, nausea, high fever (potentially with sweating and chills), anorexia, diarrhea, and myalgia are the most frequently reported side effects of overdoses or prolonged intake [58].

Bioavailability of rh G-CSF

The rh G-CSF was combined with polyethylene glycol (peg-filgrastim, lipeg-filgrastim) to extend the decay rate after injection of the rh G-CSF to approximately 30–53 hours by reducing renal excretion. This made it possible to apply only once a time and avoid daily and traumatic injections until tissue regeneration is accomplished [35].

Future embodiment and potential contributions

Regenerative techniques utilizing biological therapies, including growth factors, cytokines, and glycoproteins like rh G-CSF, which mimic the biological anabolic action, could offer a key innovation in the oncologic field, craniofacial anomaly, congenital malformations, and traumatic injuries. Researchers work to deliver ideal treatment approaches, incessantly boosting treatment outcomes. Moreover, an international collaboration of laboratories and clinics focusing on bioengineering, backed by adequate funding, is a key to driving forward cutting-edge regenerative medicine strategies.

Conclusion

Stem cell enhancement-based regenerative techniques could support the treatment of damaged tissue deterioration and/or irritated processes. Their mutual main goal should be to deliver safe, cost-effective, long-term effect restorative therapies widely applicable in translational medicine and interventional therapeutics. Furthermore, the potential regenerative properties of rh G-CSF in terms of angiogenesis, innervation, and immunity modulation could be utilized in biomedical tissue engineering applications. Hence, growth factors and cytokines additive will be expected to perform a key role, and the biomaterial will have complementary qualities that encourage cell development, tissue restoration, and infection prevention, ultimately leading to the growth of hybrid biomaterials for personalized scaffolds or tissue repair that fully restore tissue function [59].

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Conflict of Interest

The authors declare no competing interests.

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