The role of TNF-α in fracture healing in children

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Abstract

In the inflammatory stage, immune system provides the fracture site with many of immune cells as macrophages and other types, which release pro-inflammatory cytokines as tumor necrosis factor-alpha (TNF-α), interleukine-1(IL-1) and interleukine-6 (IL-6). In the present review we attempt to elaborate the role of TNF-α in fracture healing. The electronic search conducted in MEDLINE and EBASE databases which resulted in 115 studies. A total of 115 studies were screened by reading their title and abstracts, 112 studies of them were irrelevant and only three studies were included in this review. Local treatment with TNF-α at low concentration displayed pivotal role in enhancing fracture healing in human fracture bone fragments and in murine model fracture.

Keywords: Immune, Growth factor, Bone, Fracture, Children

Introduction

Fractures represent one of the major clinical problems in the world [1]. Fracture healing has been known as complex process of repair bone and surrounded tissues by primary bone healing (rigid internal fixation) and secondary bone healing which contains three main stages; inflammation, repairing and remodeling [2, 3]. As other wound repairing responses, fracture healing induces the innate immune system to release immune cells to the site of fracture. Moreover, the repair of damaged bone, requires coordinating participations of hematopoietic and many types of immune cells in the injured tissue marrow, which conjunct with the vascular and skeletal cells to regenerate the damaging in bone [4, 5]. In the inflammatory stage, immune system provides the fracture site with many of immune cells as macrophages and other types, which release pro-inflammatory cytokines as tumor necrosis factor-alpha (TNF-α), interleukine-1(IL-1) and interleukine-6 (IL-6) [6]. It was reported that, these pro-
inflammatory cytokines improved synthesis of extracellular matrix, stimulating angiogenesis and endogenous fibro-genic cells recruiting in the injury site [6, 7]. Pro-inflammatory cytokine TNF-α was reported as central mediator in inflammation response. TNF-α has two receptors TNFR1 and TNFR2, and their role in bone repair was investigated [5, 8]. It’s reported that, TNFR1 has ability to mediate inflammatory function of TNF-α which induces the inflammatory bone resorption [9]. While, TNFR2 has beneficial effect in anti-inflammatory reaction [10]. David and Schett, [11] revealed that all functions of TNF-α in bone are depending on TNFR1. The role of TNF-α in fracture healing was extensively studied. Previous studies recorded important regulatory roles for TNF-α in bone remodeling, homeostasis [12, 13]. Recently, nonessential regulating for TNF-α in bone remodeling was reported by David and Schett,[11] and TNF-α caused decreasing in osteoblast (derived from monocyte and macrophage) activity and increasing in osteoclast differentiation which accelerate the synthesis and calcification of bone [11]. Also, Abbas et al [14] displayed that TNF-α inhibited osteoblast activity via its TNFR1 receptor. Furthermore, Timmen et al. [15] concluded that from their results, the highly levels of TNF-α during chronic inflammation have a negative effect on fracture healing. In the present review we attempt to elaborate the role of TNF-α in fracture healing.

Methods

The electronic search conducted in MEDLINE and EBASE databases using keywords such as “fracture, TNF-α AND, healing and union) which resulted in 115 studies. The eligible articles that aimed to study the role of TNF-α in fracture healing in children were screened. The irrelevant articles were excluded and the results were synthesized only for 3 eligible studies.

Results

The search on the role of TNF-α on the fracture healing was carried out in PMC in the last ten years. A total of 115 studies were screened by reading their title and abstracts, 112 studies of them were irrelevant and only three studies [1, 16, 17] were included in this review. In general sample size ranged between 4 to 358 samples. The study of Glass, et al. [1] reported that, TNF-α displayed pivotal role in enhancing fracture healing in human fracture bone fragments and in open tibial fractures in a murine model. In murine model (in vivo), addition of 1 ng/mL of TNF-α at the fracture site accelerated healing, also in human fracture bone fragments, TNF-α promotes muscle-derived stromal cells (MDSC) migration and osteogenic differentiation at low concentrations in vitro. In addition to these results they revealed that, TNF-α had inhibitory effect on fracture healing when used at high concentrations. The same results were recorded by Chan, et al [16] when their results showed that, the local treatment of rhTNF at low dose (1 ng/mL) improved fracture healing but in the early phase of repair (within 24 h of injury) in fragility fractures murine model. Addition of rhTNF recorded positive effect on neutrophil recruitment and promoted recruitment of monocytes through CCL2 production. At the same time, their results demonstrated that, anti-TNF and neutrophils depletion or inhibition of chemokine receptor CCR2 impaired fracture healing.

The study of Kayal, et al. [17] showed negative effect of diabetes on fracture healing. Diabetes induced an up-regulation of proapoptotic genes during the transition phase from cartilage to bone in fracture healing. Their results revealed that, diabetes caused increasing of chondrocyte apoptosis by over production of TNF-α, the later stimulates chondrocyte apoptosis and up-regulates apoptotic genes levels through FOXO1 activation.

Discussion

Bones as complex organs represent the main supporting system for animal and human bodies, more than that there are many functions for skeletal system as hematopoesis, regulation and storage minerals and facilitation of locomotion [18]. Therefore, bone repair is an urgent needed must be
done rapidly and accurately when bone undergoes many problems as open fractures, fragility fractures (osteoporotic) and diabetic fracture [1]. During fracture healing, a cascade of events is involved; inflammatory reaction is the first one of them, occurs within minutes of bone injury [19]. In this stage, immune response provides the fracture site with immune cells as macrophages and other types, which release many types of pro-inflammatory cytokines as tumor necrosis factor-alpha (TNF-α) [6]. In this systematic review we summarize the role of TNF-α in bone fracture healing. Local treatment with TNF-α at low concentration displayed pivotal role in enhancing fracture healing in human fracture bone fragments and in murine model fracture. TNF-α was able to promote muscle-derived stromal cells migration and osteogenic differentiation which accelerate fracture healing Glass, et al. [1]. These results were confirmed by Chan, et al [16] when their results recorded that, low dose (1 ng/mL) of rhTNF improved fracture healing but in the early phase of repair in fragility fractures murine model. This effect of rhTNF was by promoting recruitment of monocytes through CCL2 production. The studies of [1] and [16] were in harmony when they reported that, the low levels of TNF-α improved fracture repair and the high levels of TNF-α had inhibitory effect on fracture healing. This was reported previously; Timmen et al. [15] Indicated to that, the highly levels of TNF-α during chronic inflammation had negative effect on fracture healing. Also, Hashimoto [20] studied the effects of TNF on the healing of fractured ribs in rats. Their results showed that, fracture healing was inhibited by daily administration of high dose of TNF (400 micrograms/kg) which caused inhibition of differentiation for mesenchymal cells into chondroblasts. The positive role of low doses of TNF-α in fracture healing is by recruitment and osteogenic differentiation of muscle-derived mesenchymal stromal cells which induced callus formation during fracture repair [1]. Furthermore, TNF-α could improve fracture healing when used at low concentration in early phase of fracture repair [16]. These results agree with that reported by [21, 22] when their results showed that, TNF-α promoted osteogenic differentiation of bone marrow derived in a time and dose dependent manner. The other included study in this review was by Kayal, et al. [17] which revealed negative effect of TNF-α in diabetes fracture healing. This effect was by over production of TNF-α, which stimulates chondrocyte apoptosis and up-regulates apoptotic genes levels by FOXO1 activation. In summary we can conclude that from consistence results obtained of included studies in this review which proved the local treatment of TNF-α at low concentration in early phase of fracture enhanced bone fracture healing.

Conclusions

Local treatment with TNF-α at low concentration displayed pivotal role in enhancing fracture healing in human fracture bone fragments and in murine model fracture

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References


