Volumetric Muscle Loss

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Volumetric muscle loss (VML) is the massive wasting of skeletal muscle tissue due to traumatic events or surgical ablation. This pathological condition exceeds the physiological healing process carried out by the muscle itself, which owns remarkable capacity to restore damages but only when limited in dimensions. Upon VML occurring, the affected area is severely compromised, heavily influencing the affected person's quality of life. Overall, this condition is often associated with chronic disability, which makes the return to duty of highly specialized professional figures (e.g., military personnel or athletes) almost impossible. The actual treatment for VML is based on surgical conservative treatment followed by physical exercise; nevertheless, the results, in terms of either lost mass and/or functionality recovery, are still poor. On the other hand, the efforts of the scientific community are focusing on reconstructive therapy aiming at muscular tissue void volume replenishment by exploiting biomimetic matrix or artificial tissue implantation. Reconstructing strategies represent a valid option to build new muscular tissue not only to recover damaged muscles, but also to better socket prosthesis in terms of anchorage surfaces and reinnervation substrates for reconstructed mass.

VML | war muscle injuries | permanent disability | prosthesis | reconstructive therapies | muscle loss | war | muscle injury

1. Introduction

The musculoskeletal system occupies the largest volume of the body, revealing the ability to self-regenerate upon tissue damage. However, its regeneration ability is limited in relation to the extent of the damage, i.e., muscular tissue fails to regenerate injuries such as extensive loss of mass, also known as volumetric muscle loss (VML) [1].

VML includes both traumatic lesions and surgical removals of a large muscle area with the associated loss of stem cells and extracellular matrices (ECMs) and the consequent impairment of regenerative capabilities [2]. VML is a common pathological condition that may occur in relation to primary trauma such as crush injuries, penetrating trauma and blasts, or secondary trauma like compartment syndromes and comorbidity to open bone fracture [3][4]. However, the frequency of VML injuries in civil and military population is disproportionate, with the latter being the most affected group. In fact, it has been estimated that among 14,500 military personnel evacuated from battlefields from 2001 to 2013, 77% reported musculoskeletal injuries [5].

In modern conflicts, injuries to limbs cover the majority of battlefield wounds. Corona and colleagues [6] collected data during the first years of the 2000s from both Operation Enduring Freedom (OEF) and Operation Iraqi Freedom

(OIF). In particular, the authors analyzed a group of retired service members with orthopedic trauma (type III tibia fracture) and a group of battlefield-injured service members who retired due to various injuries (general). In both cases, among service members medically discharged from their military occupations, muscle-related disabling conditions were reported. In particular, in the orthopedic group, 65% were affected by VML, a value higher than the general group reaching 92% of muscle-related injuries [6].

Akpoto and collaborators [7], in a study conducted from 1st May to 31st December 2014 (8 months) during the Mali conflict, examined war-related extremity injuries in 50 soldiers recovered at Togo Level two Hospital. Interestingly, most of war-related traumas were due to sudden explosive devices (36%), followed by mortar and rocket shrapnel (30%). The lesions were distributed mainly on the lower extremities (62.92%), and soft tissue wounds (skeletal muscle was the most representative) were the second most common accidents during the conflict (28.09%).

Another important complication of war trauma is heterotopic ossification (HO). This process is mediated by the complex interaction of both systemic and local wound inflammation that, upon an intricate cascade of events, leads to the formation of lamellar bone in non-osseous tissues [8][9][10]. In particular, the wound stimulate mesenchymal stem cells (MSCs) mobilization in a injury site, here the local released growth factors (BMP family) and inflammatory cytokines (IL-3, IL-6, and IL-10) promote the differentiation of MSCs in osteoprogenitors through the Runx-2-mediated pathway [11]. HO can occur in both civilian and military trauma, but the incidence is unpaired: for civilian trauma, HO formation is due to the combination of a central nervous system (CNS) trauma and mainly a fracture of the femur (54% of patients with thigh trauma) [12]. In war trauma, HO occurs with or without CNS trauma, with a high incidence rate that reaches 64%, following military blast injuries [13][14]. Nowadays, the only effective therapy for HO is surgical removal that has to be ideally performed at least six months after the injury occurs to allow for an adequately ectopic bone cortication and maturation [15]. Unfortunately, this approach generates VML in skeletal muscle tissue, inevitably compromising the functionality of the interested area. For these reasons, HO pathology represents the most significant obstacle to independence, functional mobility, and return to duty for combat-injured veterans [16].

2. Emerging Reconstructive Strategies

Soft tissue injuries, especially skeletal muscle ones, are very common in daily life. Besides military personnel exposed to a wide series of combat-related trauma [6], civilian categories such as athletes, construction workers, or simply people behind the wheel are frequently victims of these kinds of incidents [17][18]. Unfortunately, VML occurs in a large percentage of muscle-related trauma, often leading to the development of chronic disability [19]. Actual therapies consist in wound debridement and surgical reconstruction by using free muscle flaps and physical training [20]. However, in the majority of the cases, these approaches are unsatisfactory, and the recovery of both aesthetically and functionality is completely inadequate [21]. For these reasons, there is a need for reconstructive therapies based on skeletal muscle tissue engineering. Whereas preclinical studies on animal models are very promising, especially those conducted on rodents [22], actual clinical treatments based on acellularized scaffolding are not enough to achieve a promising therapeutic approach [23][24][25][26]. Thus, the real challenge today is still the jump up from these cells-based therapeutic strategies to human size. At the present time, studies on large animal

models are few, and the preliminary outcomes are not at all encouraging [27][28][29]. In addition, although the literature is exhaustive on the issues related to VML in terms of incidence [5][6][7], implication, current therapies, and emerging reconstructive strategies, some aspects need to be further investigated at a scientific level, such as consequences of volumetric loss on the prosthesis socket, the reduction of the contact surface on a prosthesis, and effects of re-innervation tagging on a reconstructed mass (Figure 1). We are confident that skeletal muscle tissue engineering is the right way to resolve the highly disabling pathology that negatively affects the quality of life of people suffering from VML-related pathologies. Furthermore, this reconstructive approach would be notably useful for replenishing prosthesis sockets and then enhance contacts and innervation surfaces for functional amelioration.

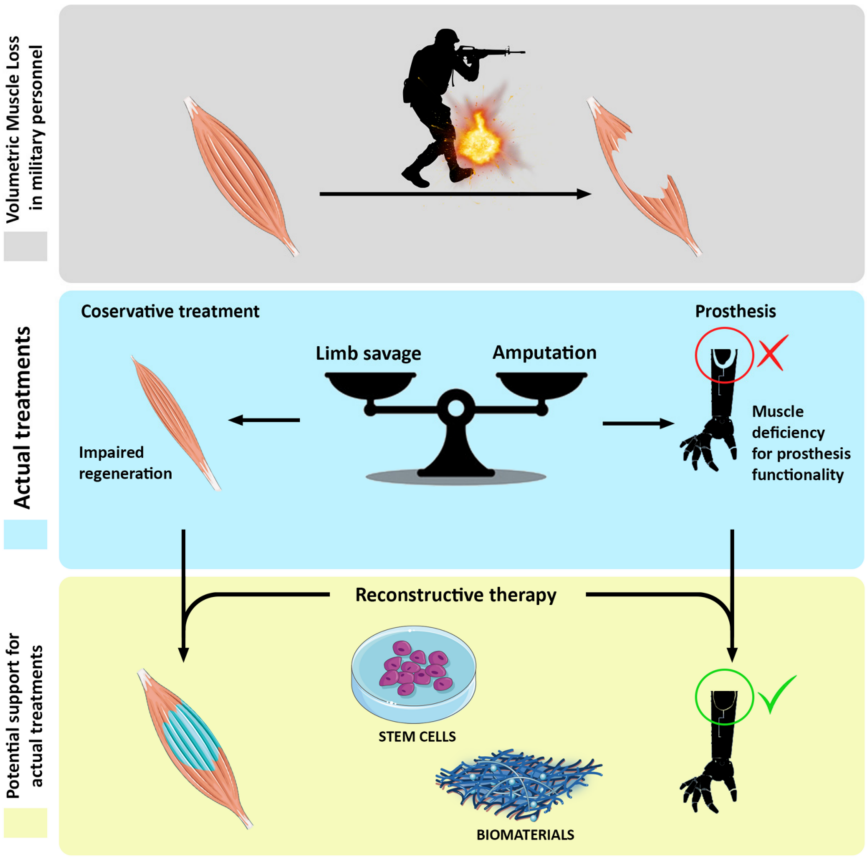

Figure 1. Schematic representation of cell-based reconstructive approach to volumetric muscle loss (VML) recovery.

However, the translation of tissue engineering strategies to clinical practice is still a challenging task. In particular, there are three main limitations to overcome: (i) finding the optimal muscle progenitor source that show both myogenic potential and high proliferation rates to obtain a sufficient amount of cells; (ii) achieving a 3D tissue with an adequate density, dimensions and cell alignment to be comparable with a native muscle tissue architecture; (iii) promoting the in vivo integration and survival of an implanted tissue through rapid vascularization and innervation [30].

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