Controlled local drug delivery strategies from chitosan hydrogels for wound healing

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ABSTRACT
Introduction: The main target of tissue engineering is the preparation and application of adequate materials for the design and production of scaffolds, that possess properties promoting cell adhesion, proliferation and differentiation. The use of natural polysaccharides, such as chitosan, to prepare hydrogels for wound healing and controlled drug delivery is a research topic of wide and increasing interest. Areas covered: This review presents the latest results and challenges in the preparation of chitosan and chitosan-based scaffold/hydrogel for wound healing applications. A detailed overview of their behavior in terms of controlled drug delivery, divided by drug categories, and efficacy was provided and critically discussed. Expert opinion: The need to establish and exploit the advantages of natural biomaterials in combination with active compounds is playing a pivotal role in the regenerative medicine fields. The challenges posed by the many variables affecting tissue repair and regeneration need to be standardized and adhere to recognized guidelines to improve the quality of evidence in the wound healing process. Currently, different methodologies are followed to prepare innovative scaffold formulations and structures. Innovative technologies such as 3D printing or bio-electrospray are promising to create chitosan-based scaffolds with finely controlled structures with customizable shape porosity and thickness. Chitosan scaffolds could be designed in combination with a variety of polysaccharides or active compounds with selected and reproducible spacial distribution, providing active wound dressing with highly tunable controlled drug delivery.

1. Introduction
Tissue repair and regeneration is an essential body ability to react against infection and preserve integrity and function. This extraordinary capacity involves the reaction of the immune system and the activation of cell proliferation and differentiation process allowing the repair of the physical damages and the restoring of the original functional capabilities. A common example of tissue repair experienced by all of us at least once in the life is represented by the wound healing process.

Wound healing is a highly complex skin process involving defined steps from vascular response and blood coagulation, to formation of fibrin network, re-epithelialization, collagen maturation, and remodeling of connective tissue [1]. In such a complex system, the definition and classification of the wound types are still under scientific discussion and improvement and a plethora of definitions have been proposed. Among wounds, attention can be focused on the acute and chronic types (Table 1) depending on the healing time. Acute wounds derive mainly from mechanical injuries or surgical interventions and are usually managed efficiently with good chances of success in a time frame of some weeks. On the other hand, wound healing is not always a granted process and dysfunctional skin responses can result in tissue repair failure. Chronic wounds are traditionally divided etiologically, since, apart from burn wounds, they are more and more associated to age-related pathologies, such as diabetes (i.e. diabetic foot ulcers), vascular insufficiency (i.e. venous leg ulcers), prolonged decubitus, or cancer. The underlying impairment deriving from these pathologies negatively contributes to the resolution of those sores, which fail to proceed through an orderly and timely reparative process to restore the functional and esthetic status of the tissue over a period of 3 months [2].

Another classification is to evaluate if the wound is cleaned or infected. In association with the wound stage, type of treatment, skin aging, nutrition, and glycemic level, it is well known that impaired healing of chronic wounds strongly depends by bacterial burden [3]. Pooling microorganisms (microbiomes) can colonize and grow in wounds bringing to severe infection-related complications, such as amputation (i.e. diabetic foot ulcer) or sepsis and death. Staphylococcus, Pseudomonas, Corynebacterium, and Anaerococcus are examples of the ten most abundant bacterium genera found in chronic wounds. On the other hand, microbiome can be exploited as diagnostic tool in wound treatment to modulate therapies, as easily accessible and highly reactive information site. Recent studies demonstrated that wound depth and duration are associated with different microbial variety and loading. For these reasons, it is of pivotal importance to characterize the microbiome to distinguish between benign...