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1. Introduction

Chronic wounds are widely recognised as a global health challenge, but both our understanding of wound biology and the implementation of technological innovations for their treatment have made only limited progress in the last few decades [1]. Currently, the clinical assessment of the wound is based on the experience of the clinicians who follow recommendations taken from a range of available guidelines and choose commercially-available wound dressings on the basis of their suitability to the wound conditions [2]. For example, the Wounds UK's best practice statement on the management of chronic wounds recommends several criteria for the assessment of lesions that are mainly based on a subjective clinical inspection of the overall wound bed and peri-wound area status (e.g. inflammation), the exudate volume and viscosity, pain, and infection-generated malodour. Methods of wound size measurement provide quantitative data, but they suffer of limited intrarater reliability. Likewise, the choice of the most suitable wound dressing is made with the aim of providing biological conditions favourable to healing. Despite the wide range available, wound dressings are all designed with two main characteristics; (i) an absorbent layer made of a polymeric porous hydrogel capable of absorbing excess exudate while keeping the wound moist and (ii) a film (e.g. silicon) protecting the wound from external contaminants and bacteria [3]. More advanced wound dressings include anti-microbial agents (e.g. silver nanoparticles) or growth factors known to promote healing [3]. The use of the latter is limited by their costs, need for refrigerated storage conditions and debated healing properties.

In this context, up to 42% of wounds do not heal within six months from the first presentation, often leading to severe complications [4]. Based on these premises, the quest for both healing-promoting wound dressings and objective parameters of wound evaluation is legitimately advocated.

2. Theranostic Wound Dressings

It is here proposed that technological progress can emerge from the consolidated, yet often ignored, knowledge about the interactions occurring between biochemical factors and cells and the surface of biomaterials to develop a platform for innovative theranostics; i.e. devices that, unlike traditional dressing merely protecting and keeping moist the wound, will be capable of healing and outputting readable biochemical and cellular biomarkers.

2.1 Forgotten lessons of biomaterial biocompatibility

It has been demonstrated that the levels of pro-inflammatory cytokines (i.e. IL-1, IL-6, IL-8, TNF-α) are higher in chronic wounds than in healing wounds [5]. As far as the search for cellular biomarkers is concerned, excessive infiltration of ulcers by neutrophils, cells usually associated with the acute inflammatory response, appears to be instead responsible for the chronic inflammation characteristic of non-healing wounds [6]. A link between the activation of these cells and the occurrence of a chronic wound may be potentially found in the ability of neutrophils to release significant amounts of enzymes such as the collagenase

that is responsible for the destruction of the connective tissue matrix and of the elastase, an enzyme that is capable of hydrolysing important healing factors such as PDGF and TGF-ß [7].

Although of high interest, these findings have not been linked to the well-established principles of biomaterial biocompatibility that demonstrate as the biomaterial surface properties can lead to the adsorption of a wider range of proteins. These proteins play a role either in the cellular biochemical signalling pathways (i.e. pro-inflammatory cytokines, growth factors) or as structural components of the extracellular matrix of tissues (e.g. fibronectin, laminin). Depending on the hydrophobic and electrostatic interactions and hydrogen bonds occurring upon adsorption on polymerics surface, these proteins may either retain their native conformation or undergo denaturation. In the former case, they maintain their biochemical role of either cell signalling or substrates. In the latter case, they are likely to become antigens capable of activating immune cells, thus protracting the inflammatory response into a chronic status [8*]. In the case of the biomaterials used for manufacturing the absorbent layer of wound dressings, the absorption throughout the mesh of the hydrogels can lead to an additional phenomenon that is the concentration of either favourable or unfavourable proteins and cells within the wound bed. It is therefore argued that a systematic study of the interactions between the biochemical and cellular components of the exudate and the wound dressing biomaterials could indeed drive the development of theranostic wound dressings. It is suggested that these developments could focus on the surface functionalisation of the currently used biomaterials rather than searching for completely new solutions. This is the approach that the authors will be following at the Centre for Regenerative Medicine and Devices (CRMD), University of Brighton through a 6-year research project supported by the UK Research and Innovation, Engineering and Physical Science Research Council (EPSRC).

2.2 Harnessing biomaterial biocompatibility knowledge for the development of healing-promoting wound dressings

2.2.1 The clinical approach

The development of biomaterials able to promote healing needs to consider the current clinical protocols. Typically, the clinicians' approach is to minimise the disturbance of the wound bed over the course of the treatment. The preferred route is to start the treatment at the first visit by the application of a primary dressing made of a synthetic, relatively hydrophobic polymer of limited swelling properties that is interposed between the wound bed and the secondary dressing that is a material more hydrophilic and therefore with relatively higher swelling properties. While this approach enables the control of the wound environment by simultaneously keeping the wound moist and reducing the exudate volume, the interaction with the relatively more hydrophobic surface of the polymeric fibres of the primary dressing may cause the denaturation of proteins thus exacerbating the inflammatory reaction. However, as these dressings are removed after 2 or 3 days, their potential long-term negative effect is likely to be limited. Wound dressings based on natural biopolymers including methylcellulose (cellulose of varying swelling properties for the treatment of wounds with moderate or excessive exudate volumes) and alginate (mainly for bleeding wounds) are used throughout the treatment until the wound margins are closing. In this last phase biomaterials with relatively limited swelling properties are applied. Also, the periodic change of the dressing has to minimise the disturbance of the healing tissue.

2.1.2 The proposed technological solution

The modification of the surface of the wound dressing biomaterials can be designed to enable the clinicians to maintain their protocols while exerting a healing action. For example, the surface of the fibres of the relatively hydrophobic primary dressing materials could be enhanced by established engineering methods (e.g. electrospinning) [9] and modified to expose anti-fouling agents minimising the adsorption and denaturation of proteins. Hydrophilic hydrogels making the absorbent layer could be modified to dock preferentially growth factors and tissue cells rather than cytokines and inflammatory cells. These features, if coupled with a relatively fast degradation (from 2 to 7 days), could accelerate the healing process by creating a favourable micro-environment within the wound bed while preventing its disturbance upon removal of the dressing. Likewise, the presence of anti-fouling and novel anti-bacterial agents [10] could reduce the establishment of bacterial biofilms thus minimising the risk of infections.

2.2 Harnessing biomaterials biocompatibility knowledge for prognostic wound dressings

2.2.1 Potential healing biomarkers

Oxygen and pH have been identified as useful parameters to assess wound improvement or deterioration. It has been shown that a more alkaline pH (7.15-8.90) is indicative of non-healing wounds whilst an acid pH, or closer to neutral, suggests higher healing rate [11]. Likewise, a hypoxic environment (5-20 mmHg) is likely to prevent collagen deposition, epithelialisation, angiogenesis and resistance to bacteria [12].

Colorimetric methods to assess these biomarkers are either qualitative or rely on equipment of limited accuracy. Electrochemical sensors are relatively more expensive and difficult to integrate in the wound dressing structure [13].

2.2.2 Candidate Sensing Systems of Biomarkers

The swelling properties of most of absorbent layers and/or the ability to modify polymer surfaces with molecules able to interact specifically with relevant biochemical and cellular biomarkers offer an opportunity to transform the retrieved dressing from disposable waste into useful sensor chips for the monitoring of the wound state. Upon removal from the wound, dressings could be sprayed with fluorophore-tagged antibodies to provide immediate qualitative analysis to be visualised in a portable black box. Alternative quantitative measurements of the biomarkers could be obtained through the optimisation of operator-friendly exudate elution kits where proteins and cells can be rapidly extracted from the dressings and analysed by conventional methods (e.g. ELISA, flow cytometry). Likewise, a systematic transcriptomics study of dressing-absorbed wound exudates could pave the way towards the development of micro-arrays to define wound status [14].

3. Future Perspectives

Synthetic biomimetic biomaterials have emerged as strong candidates to enhance biointeractions at the surface of biomaterials [15**]. Their ability to control cell activities and dock specific proteins, as well as their suitability to be formulated as either surface functionalisation molecules or hydrogels, make them suitable candidates for the development of theranostic wound dressings. Researc at the CRMD aims to harness this potential by combining a systematic clinical study of dressing effects on exudate composition and wound healing for the development of new theranostic devices.

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15. Santin M, Phillips G ed. Biomimetic, Bioresponsive, and Bioactive Materials: An Introduction to Integrating Materials with Tissues. Wiley & Sons 2012 Print ISBN:9780470056714, Online ISBN:9781118129906, DOI:10.1002/9781118129906. ** This book provides an overview on biomimetic biomaterials and their biocompatibility that could drive the development of novel theranostic wound dressings.