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Review article

The quest for tissue repair's holy grail: The promise of wound diagnostics or just another fishing expedition?

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ABSTRACT

In both Celtic and later Norman Arthurian legend, the Fisher King was a man charged with keeping and protecting the Holy Grail. He suffered from perpetual non-healing wounds, which could only be healed once the hero and most worthy of knights, Perceval, could answer the question "who does the Grail serve?" In this manuscript, we ask the same question in a slightly more modern context. It has become evident that perpetually using empiricism and clinical guesswork alone is insufficient to improve tissue repair beyond its present state. Real time or near-real-time diagnostics and theragnostics to identify progress are essential adjuncts to realize real improvements. We review recent and near-future advances in whole-genome sequencing, community profiling, inflammation measurements, peri-wound receptor viability, pH and regional perfusion indices as potentially promising interim sites to measure. In this manner, by measuring what we manage, perhaps we can avoid costly fishing expeditions and help our patients heal. This is a quest that we feel is not only noble, but also essential.

Contents

1. Introduction

In both Celtic and later Norman Arthurian legend [1,2], the Fisher King was a man charged with keeping and protecting the Holy Grail [3] (Fig. 1). He suffered from perpetual non-healing wounds, which could only be healed once the hero and most worthy of knights, Perceval, could answer the question "who does the Grail serve?"

In tissue repair and wound healing, in many ways we follow in the line of Perceval and remain on a Grail quest of our own. We have been blinded by the temptation of single, simple cures when the reality of this quest might be far more nuanced. We have not had a method to measure our progress from step to step so we often find ourselves lost on the journey. This brief manuscript will detail promising tools in several discrete areas of microbiology (functional metagenomics, community profiling), histology (inflammation assessment, pH) and local perfusion (implantable sensors, real-time imaging) to assist us on this quest and help us measure what we manage.

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Fig. 1. The wounded Fisher King [34].

Chronic wounds, particularly in diabetes, pose a serious risk for lower extremity amputation as up to 85% of diabetes-related amputations are preceded by foot ulcerations [4]. The 5-year mortality rate in patients who have undergone a diabetes-related amputation is close to 50% which is comparable to some types of cancer [5,6]. Furthermore, the treatment of these complications has been proven to be very costly [7–9]. These risks and facts underscore the importance of undertaking appropriate screening and intervention [10,11]. It is remarkable, therefore, that there exists such a dearth of established classes of validated therapies for wound healing in general and diabetic foot wound healing specifically. With most other chronic conditions, there exists a method of defining and establishing the severity of disease and treating it to certain measurable tests. For instance, cardiovascular disease consists of many established classes of therapy such as HMG CoA reductase inhibitors, antihypertensives, and inotropes. Each of these has methods to define and measure its effect (cholesterol, blood pressure, cardiac output).

2. Are there measurable targets to guide the treatment of diabetic foot ulcers?

In order to develop categories of treatment of diabetic foot ulcers, we require targets for treatment. A potential characteristic and measurable target includes evaluating wounds from a microbiology perspective with polymerase chain reaction (PCR)-based identification of multiple bacterial species from wound biopsies. Other measurable characteristics include the pH value of chronic wounds or evaluating the role of matrix metalloproteinases. Perhaps there are advanced measurable targets for evaluating local blood flow or receptor viability to determine sufficient wound debridement. We review these contemporary and potential measurable targets that may provide indicators of what constitutes a "healthy wound" and ultimately guide effective treatment strategies.

3. DNA-based diagnostics for identifying bacteria and drug resistance in wound colonization

There are new molecular technologies that can detect and monitor pathogens more rapidly and more accurately compared with the traditional clinical microbiology methods, such as culture-based techniques that were developed by Pasteur 150 years prior [12]. One of these methods is PCR-based identification of bacterial wound colonization. PCR is a molecular method to amplify a genomic region of interest. A small subunit ribosomal RNA (rRNA) gene in bacteria, called 16S rRNA, is a useful gene target that is conserved across all bacteria [13]. This 16S rRNA