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Molecular finds of pressure ulcer: A bioinformatics approach in pressure ulcer

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ABSTRACT

Background: Understanding the biological processes underlying Pressure Ulcer (PU) is an important strategy to identify new molecular targets. Bioinformatics has emerged as an important screening tool for a broad range of diseases.
Objective: This study aim of the current study is to investigate the protein-protein interaction in the PU context by bioinformatics.
Methods: We performed a search in gene databases, and bioinformatics algorithms were used to generate molecular targets for PU based in silico investigation. Interactions networks between protein-coding genes were built and compared to skin.
Results: TNFA, MMP9, and *IL10* genes have higher disease-related connectivity than a connectivity general global. *MAGOH*, *UBC*, and *PTCH1* as were leader genes related to skin. Ontological analysis demonstrated different mechanisms associated, such as response to oxidase stress.
Conclusion: TNFA, MMP9, and *IL10* are possible therapeutic targets for pressure ulcer. Additional investigation of cell post-transcriptional machinery should be investigated in PU.
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1. Introduction

Pressure ulcers (PU) are also known as decubitus ulcers, or bedsores lesions. PU develops in consequence of prolonged periods of continuous pressure on the skin leading to areas of tissue necrosis [1]. Pressure ulcers lead to significant health problems, such as pain, functional and aesthetic, leading to disfigurement area [2,3]. Also contributing to the increased risk of medical complications [4]. The main factors for PU development are intensity and duration of pressure [5]. Elderly, victims of stroke, diabetics, those with dementia boards and people who use wheelchairs or bedridden with any change in mobility or sensitivity are the most committed by PU [6,7]. The majority of patients affected with PU are those having health conditions that lead to immobility for prolonged periods of time [1,8]. On the other hand, even thirty years after the publication of the first clinical guidelines for prevention of this type of injury incidence rates remain high [9], PU treatment still complex and challenging [10].

Recently, molecular biology has been impacted the understanding of the pathogenesis of several diseases including PU [11–13]. Specifically, inflammatory cytokines play a major role in the etiology of pressure ulcers, relating to increased expression of genes related to them and tissue damage in areas subjected to pressure [14]. The risk to develop PU may be attributable to the individual differences in response to inflammatory stressors [15]. Inflammatory mediators [16], such as interleukin 1A (IL1A), IL1B, IL1 receptor antagonist (IL1RA), IL-6, IL10, and tumor necrosis factor-α (TNFA) are associated with the PU development [17–20].

Bioinformatics has emerged as an important screening tool for a broad range of diseases [21–23]. Specifically, Bioinformatics is useful for analysis of genomic and proteomic using web-based databases [24,25]. For example, Bioinformatics was recently used to characterize two distinct inflammatory diseases that present the

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same etiological factors [21]. Considering the complex nature of PU pathogenesis, the purpose of the current study was to perform a Bioinformatics analyze of PU.

2. Material and methods

2.1. Genes selection

The Bioinformatics approach was described previously [21,24]. Briefly, the first step has identified the genes associated with PU according to MEDLINE database based on the Medical Subject Headings (Ulcer pressure, Decubitus Ulcer, bedsore and Pressure Ulcer). Search criteria were the inclusion of each Medical Subject Headings and the keyword gene to generate a list of genes associated to PU. We also searched in Genecards database (www.genecards.org) [26]. A search for the term skin only in Genecards (www.genecards.org) [26] to create a control group to compare with PU. As a second step, first gene lists for PU and control were expanded. Network expansion was performed using STRING (version 10) [27–29]. STRING (version 10) [27–29] is a biological web resource database to predicted protein–protein interactions. Only predicted associations with a higher level of confidence (results with a score ≥0.9) were selected. The Weighted Number of Links (WNL) represents the gene interactions in a specific network. WNL is obtained by the sum of all interactions on the specific network multiplying to 1000 [21,23,30]. On the other hand, Total Interaction Score (TIS) represents all gene interactions in the entire STRING database. To obtained TIS value, all interactions of a gene in the whole STRING database were summed and adjusted by multiplying to 1000.

2.2. Statistical analysis

Analyses were performed using SPSS carried out in SPSS (Version 18.0, IBM, New York, NY, USA). Kolmogorov-Smirnov and the Shapiro-Wilk Tests were conducted to evaluate data distribution. Samples presented as a normal distribution. Statistical significance was accepted at $p < 0.05$. According to WNL and TIS, all genes were clustered, using K-means Clustering [23,30]. Genes with no interactions were orphan genes [21,24]. After K-Means Clustering, ANOVA, and Tukey- Kramer post hoc tests were applied to certify the results. Genes with no interactions were defined as orphan genes [22,30]. The category with higher WNL and lower TIS was considered as therapeutical targets. All other classes apart from leader genes were not taken into account for analyses purpose.

2.3. Topological and ontological analysis

Cytoscape [31] is a software platform was used for visualization of molecular interaction networks. All topological analyses were carried out with Cytoscape [31] to evaluate both networks. Biological Networks Gene Ontology (BiNGO) tool is Cytoscape plugin

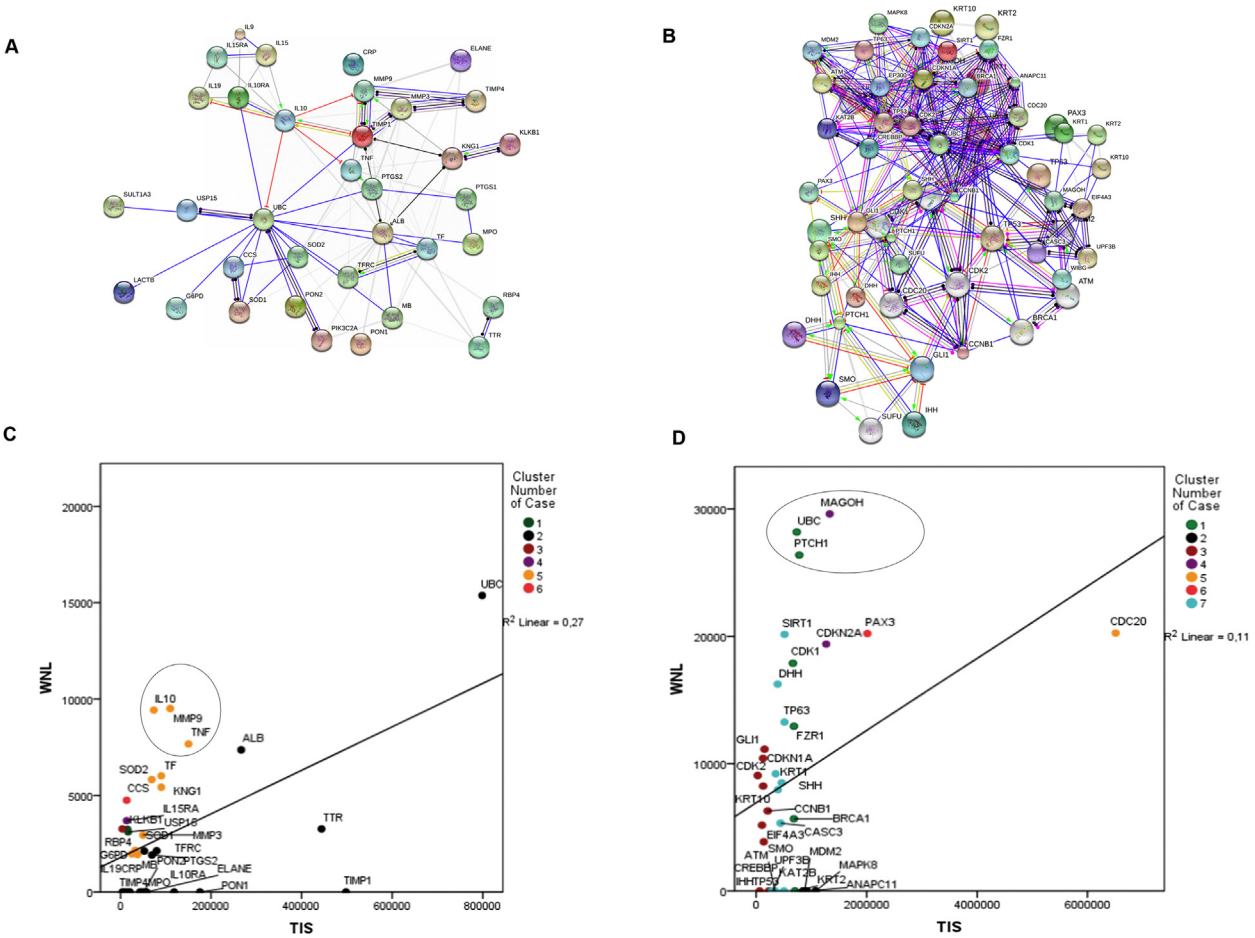

Fig. 1. Comparative networks of Pressure Ulcer and Skin. STRING networks of in A Pressure Ulcer and B Skin. In C and D scatter diagrams are showing condition-related connectivities (WNL, weighted number of links) versus the global connectivities (TIS Interactions Total Score). The leader genes and clusters Pressure Ulcer and Skin were presented in C and D respectively. *TNFA, MMP9* and *IL10* genes presented higher WNL and lower TIS in PU. On the other hand, *MAGOH*, *UBC*, and *PTCH1* were associated with skin.

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