GENE EXPRESSION PROFILING IN SKIN AND BLOOD IN HIDRADENITIS SUPPURATIVA

J.L. Blok¹, K. Li²; C. Brodmerkel²; B. Horváth¹, M.F. Jonkman¹

¹ Department of Dermatology, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands
² Janssen Research & Development, LLC, Spring House, PA, U.S.A.

Submitted
Hidradenitis suppurativa (HS) is an inflammatory skin disease characterized by recurrent abscesses, nodules and sinus tract formation that is mainly localized in the body folds. The pathogenesis of HS is poorly understood. Mutations in genes encoding for essential compounds of the transmembrane protease γ-secretase, including NCSTN, PSEN1 and PSENEN, have been identified in familial HS. These mutations may result in impaired Notch signaling promoting cyst formation and continuing inflammatory activity. Additionally, certain single nucleotide polymorphisms (SNPs) at the promoter region of the tumour necrosis factor - alpha (TNF-α) gene were found to be associated with a greater susceptibility for the development of HS as well as to influence the natural course of the disease. Furthermore, elevated levels of IL-1, TNF-α and IL-10 were demonstrated in both lesional and perilesional skin of HS patients, and increased expression of the IL-23/Th-17 pathway was found in lesional skin. However, the mechanism behind these pro-inflammatory changes in HS is still largely unknown.

To acquire a better understanding of the molecular pathogenesis of HS, we performed mRNA microarray studies to compare gene expression in lesional skin to healthy skin of HS patients. Also, the gene expression profile in whole blood of patients and unaffected individuals was determined.

Seventeen HS patients were included. Whole blood was collected from all subjects and ten healthy controls. Skin biopsies of 3 mm were obtained from inflammatory lesions in all 17 patients. Additionally, an extra biopsy from clinically healthy skin of the upper arm or leg was obtained from 13 patients. The skin samples were immediately frozen in liquid nitrogen and subsequently stored at -80 degrees Celsius. mRNA was extracted from skin samples using the Qiagen RNeasy Fibrous Tissue Mini Kit (Qiagen Inc., Valencia, CA) and from whole blood with the Qiagen PAXgene blood RNA kit according to the manufacturer’s instructions. RNA was hybridized to the GeneChip HT HG-U133+ PM Array (Affymetrix, Santa Clara, CA). Pathway analyses were conducted with QIAGEN’s Ingenuity Pathway Analysis (IPA®, www.qiagen.com/ingenuity). Array Studio software version 8.0 (OmicSoft Corp., St. Morrisville, NC) was used to analyze microarray data. Dysregulated genes were identified using a general linear model. Expression modulation with a fold change >2 or <2 and an FDR-adjusted p-value < 0.05 were considered significant.

A significant difference was observed in mRNA expression between lesional and clinically healthy skin of HS patients, with over 1145 probe sets representing over 800 genes having at least a two-fold change (p <0.05). Patients with the most dysregulated gene profile were more likely to have longstanding disease (>15 years) (figure 1a). Pathway analyses of the modulated genes were mostly related to inflammation, including cell adhesion, diapedesis and
extravasation as well as immune cell signaling and communication pathways (figure 1b). An interesting finding is involvement of the atherosclerosis signaling pathway in lesional HS skin as it supports the current thought that the inflammatory response in HS is associated with metabolic syndrome. Expression of NCSTN, PSEN1 and PSENEN was not modulated in lesional compared to clinically healthy skin of patients. No significant differences were identified in whole blood mRNA expression between patients (N=17) and healthy controls (N=10) (data not shown).

In summary, we demonstrated significant altered gene expression in lesional HS skin compared to clinically healthy skin of patients. This, in addition to the finding that whole blood RNA expression did not differ between HS patients and healthy subjects, implicates that activated cells in HS reside in affected tissue. This may be due to migration of leucocytes from the circulation into skin tissue in response to released inflammatory chemokines. Our results implicate that the inflammatory reaction is restricted to the skin of specific anatomical areas and HS may therefore be considered as a localized rather than a generalized skin disease. However, our results must be interpreted with caution as the sample size was relatively small. Regardless whether local dysregulation of the atherosclerotic pathway is caused by the inflammatory process or a secondary event due to an unhealthy lifestyle, the clinician should be aware of metabolic syndrome in HS patients as early detection and treatment may prevent cardiovascular complications. As perilesional skin of HS patients already shows histological abnormalities, one may hypothesize that the skin type of HS patients in general is genetically different from normal human skin, making patients prone to the development of HS lesions under certain mechanical and lifestyle triggers. Therefore, investigating differences in gene expression between clinically healthy skin from predilection sites of HS patients and skin of unaffected individuals from the same sites would be an interesting additional study.
Figure 1. (a) The heat-map of differentially expressed genes in HS skin based on mRNA microarray analysis. A significant difference was observed in mRNA expression between lesional (grey boxes) and non-lesional patient skin (red boxes). Patients with the most dysregulated gene profile were more likely to have longstanding disease. (b) The top ten canonical pathways involved in the disease profile of patient skin.
REFERENCES


