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MOLECULAR DIAGNOSIS OF INTERSTITIAL CYSTITIS

Hypothesis / aims of study

Interstitial cystitis (IC), a progressive chronic bladder disease with an increasing incidence, is diagnosed by subjective symptoms in combination with cystoscopic and histologic evidence. Often, at the time point of diagnosis the patient has gone through an ordeal of symptomatic and expensive therapies. The aim of our studies is the development of an objective molecular diagnostic assay for IC based on ten to twenty characteristic IC-markers.

Study design, materials and methods

Urine and bladder biopsies have been collected from five patients with IC and six control patients. Total-RNA was isolated from bladder biopsies and analyzed by GeneChip expression arrays (Affymetrix). Based on these results the presence of particular proteins in urine was determined by ELISA.

Results

In GeneChip expression arrays IC-patients and healthy controls have been compared: 31,000 out of over 54,000 tested probe sets showed a positive signal (detection p-value < 0.05). The difference between the two groups was significant for over 4,000 signals (t-test p-value < 0.01), and approximately 2,000 of them (corresponding to about 1,000 genes) showed an IC-to-healthy expression ratio greater than two. The IC-pattern had similarities to patterns from immune system diseases, lymphatic and rheumatic diseases (GeneGo analysis). The dominant biological processes were the immune and inflammation reactions. The array data provided a basis for detection of specific proteins in urine: the presence of seven out of nine tested proteins could be verified specifically in IC-patients. Another analysis of the array data compared inflamed (Hunner's ulcer) and not-inflamed tissue of IC-patients. The difference in over 1,900 probe sets was found to be significant (t-test p-value < 0.01), and more than 500 of these showed an ulcer vs. not-inflamed ratio greater than two. The difference was roughly limited to the processes of cell-adhesion and proteolysis, and focused on the extracellular matrix.

Interpretation of results

Comparison of IC-patients with healthy controls revealed approximately 1,000 genes with an IC-to-healthy expression ratio greater than two. Many of the up-regulated genes were expressed in leukocytes, suggesting that leukocyte invasion into the bladder wall is a dominant feature of IC. Furthermore, a comparison of ulcer and not-inflamed tissue of IC-patients resulted in clear differences in the expression of genes, of which the gene products are localized in the extracellular matrix. This result agrees with the known tissue remodelling and degradation of the bladder wall in IC.

Concluding message

GeneChip expression arrays provided a global picture of IC. The quantification of specific proteins in urine potentially allows the development of a diagnostic array for IC and will pave the way for early detection of this debilitating bladder disease and the development of rational therapies.

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<i>Is this a clinical trial?</i>	No
<i>What were the subjects in the study?</i>	HUMAN
<i>Was this study approved by an ethics committee?</i>	Yes
<i>Specify Name of Ethics Committee</i>	Kantonale Ethikkommission des Kantons Thurgau (Ethics Commission of the Thurgau Region, Switzerland)
<i>Was the Declaration of Helsinki followed?</i>	Yes
<i>Was informed consent obtained from the patients?</i>	Yes