Genetic expression profile in the prognosis of mycosis fungoides

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Introduction and objectives

Mycosis fungoides (MF) is the most frequent T cell cutaneous lymphoma.[1]
Early stages have an excellent prognosis with excellent survival rates. However there is a 20-40% risk of progression after 20 years in those patients.[2-3] Conversely advanced MF has much a worse prognosis.[2-5]

Being able to know which patients will progress and which will remain as an early MF would be tremendously useful for clinicians. Therefore the objective of our study is to find out if there is information in the diagnosis samples of MF patients diagnosed at early stages that can help us differentiate patients at risk.

Material and Methods

We collected data from a historic cohort of 57 patients with early stage MF diagnosed between 1999- 2002. A cDNA microarray was performed on these samples using the CNIO (oncologic investigation national centre of Spain) Onco-Chip. This chip includes 6386 cancer-related clones. We used the data from the microarray and confronted it with the follow up of these patients. Data was collected from clinical records and an informed consent was signed.
The patients had a medium of 14 years of follow-up and were divided in two groups: progression (development of tumour, nodes, erythroderma, blood involvement or metastasis) and no progression.

Since the samples and the microarrays were processed in two different years the initial set of 57 patients was divided in two groups of 29 and 28 patients due to the heterogeneity of the sample array results.
Relationship between genetic expression and progression was studied using GSEA.

Results

After GSEA we found significantly enriched pathways related with chemotactic activity and lymphocyte activity. Also patients that did not progressed had enriched activity in the UV response pathway probably related with the capacity of response to phototherapy.
Other pathways up regulated in progression were ERK5, AKT and PIK3CL1. Genes such as PIK3CA and PIK3R1 are repeatedly upregulated.
IFNAR1 pathway, related with JAK activity was downregulated and also P53.
The volcano pot analysis showed no results in the subgroup analysis, however taking both groups together it showed an increased expression of PPP1R3C, a gene that codifies the protein targeting of glycogen (PTG) however this data should be taken with caution.

Pathways related with progression:

CXCR4 pathway (p 0,000) Normalized Enrichment Score (NES) 1.91, FDR 0,027 genes: BCAR1, PXN, PIK3CA, PTK2, PIK3R1, PRKCA, HRAS, RAF1, CXCL12, PIK3C2G, GNB1

Other pathways with p < 5% were:
ERK5 pathway P 0,035, NES 1,15, FDR q 0,92 : genes PIK3CA, PIK3R1, HRAS, RPS6KA1, SHC1.
AKT pathway p 0,049, NES 1,52, FDR q 0,70 : genes PIK3CA, PIK3R1, GHR, CASP9, YWHAH.
Cytokines pathway p 0,034, NES 1,49 y FDR q 0,66 : genes SOCS6, SOD2, CCL2.
PIK 3-CL1 pathway p 0,035, NES 1,39, FDR 0,63 genes: PIK3CA y PIK3CD
INFAR1 pathway p 0,012, NES -1,51, FDR 1. genes: IFNAR1, JAK1, IFNAR2.
P53 pathway p0,032. NES -1,48, FDR 1. genes: MDM2, ABCB1, TP53

Pathways related with no progression:

Lymphocyte pathway (p 0,000), FDR 0,31 NES -1,67 genes: ITGA, ITGB1, SELL, SELP
UV response pathway: p 0,007, NES 1,62, FDR 0,40. Genes: NTRK3, CCNE1, RAB27A, LYN, CEBPG, IL6ST, GAL, PSMC3, RRAD, ATF3, SOD2, BAK1, STIP1, GCH1, BMP2, PRKCD, RFC4, E2F2, IRF1, RASGRP1, BTG3, CDKN1C, ATP6V1F, CHKA, EIF5, POLE3, CDC5, UROD, CDC34, NR4A1, ENO2, JUNB, SLC6A8, DNAJB1, IGFB2, CDK2, PPIF, ABCB1, RXRB, PPT1, SPOP, KIT, MET, EIF5, FURIN.

Other pathway with p < 5% was:
ERK pathway p 0,048, NES -1.48 y FDR q 0,93. Genes: SRC, NGFB, HRAS; IGF1R, RPS6KA1, MYC, EGFR, RAF, SHC1, PDGFRA, GNB1, STAT3, NGFR, ITGB1, GNAS.

Volcano Pot

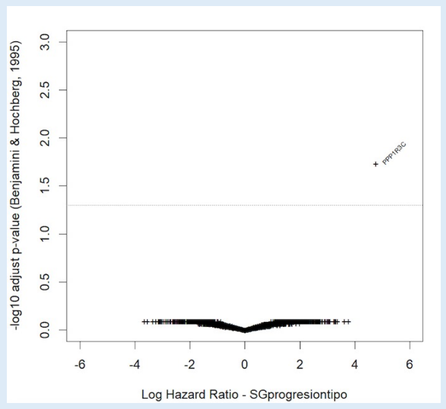

Fig.1 Volcano Pot graphic showing and increased expression of PPP1R3C associated with progression

Discussion and conclusion

Our group has demonstrated a tendency towards the expression of several pathways that is already known they are differently expressed in MF patients, such as JAK/STAT, MAPK/ERK and PIK/AKT.[6]
There are previous data of genetic expression related with progression, however it mostly refer to a advanced MF. Regarding the PIK3/AKT pathway, it has being shown that the expression of pAKT, 4E-BP1 y p-p70S6K are associated with worse prognosis.[6] Also the expression of PTEN, acting as an PI3K inhibitor has been related to better prognosis.[7]
The expression or 4E-BP1, is not only associated with the PIK3/AKT pathway but also with ERK and there is a positive correlation between p-ERK and 4E-BP1. [7]
NOTCH expression has been related to worse prognosis and it also functions as a AKT up regulator.[7,8]
High levels of TP53 are also associated with worse prognosis in advanced stage.[9]
It is important to remember that these pathways are not isolated and there is a crosstalk between them, for example AKT has been related with expression of STAT3[7,10] and NOTCH can regulate AKT.[11] Regarding early MF there is recent evidence that the expression of ZEB1 and inhibition of Twist1 can be related with better prognosis.[12]
PTG expression can increase levels of glycogen stimulating the mTOR pathway.[13]

Although our sample size was limited, we believe that pathways related with JAK/STAT, PIK/AKT/mTOR, MAPK/ERK, and cellular cycle can be differentially expressed in patients that will progress to advanced MF from the early stages of mycosis fungoides. Further studies are necessary to validate our results.

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