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AB0172 PGC-1A REGULATES AUTOPHAGY TO PROMOTE FIBROBLAST ACTIVATION AND TISSUE FIBROSIS

Y. Zhang[1], K. Dreißigacker[1], D. Distler[1], A. H. Györfi[1], C. Bergmann[1], X. Zhou[1], L. Shen[1], I. Ludolph[1], R. Horch[1], A. Ramming[1], G. Schett[1], J. Distler[1].
[1]*Friedrich-Alexander University of Erlangen-Nürnberg, Erlangen, Germany*

Background: Peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α) is the best studied member of the family of coactivators. PGC-1α was initially identified through its interaction with PPARγ in brown adipose tissue. Recent evidence further indicates that PGC-1α may also modulate the transcription of autophagy-related genes, which has recently been shown to be required for fibroblast-to-myofibroblast differentiation under fibrotic conditions. However, the role of PGC-1α in the pathogenesis of SSc has not been investigated.
Objectives: The aim of the present study was to evaluate the role of the coactivator PGC-1α on autophagy and to evaluate its role in the pathologic activation of fibroblasts in SSc.
Methods: Expression of PGC-1α was analyzed by RT-PCR, Western blot and immunofluorescence. Modulation of autophagy was analyzed by reporter studies by expression of autophagy related genes. The effects of PGC-1α knockdown on collagen production and myofibroblast differentiation were analyzed in cultured human fibroblasts and in two mouse models with fibroblast-specific knockout of PGC-1α.
Results: PGC-1α overexpression was detected by immunohistochemistry in skin sections of SSc patients and in experimental fibrotic murine skin, particularly in fibroblasts. Knockdown of PGC-1α inhibited the stimulatory effects of TGFβ on fibroblast activation with impaired induction of collagen as compared to control fibroblasts. Fibroblasts specific knockout of PGC-1α ameliorates experimental fibrosis in bleomycin-induced and adTBR-induced murine dermal fibrosis with decreased dermal thickness, hydroxyproline and myofibroblast counts compared to wild-type fibrotic mice. Incubation of dermal fibroblasts with TGFβ activated autophagy in control fibroblasts with increased expression of the autophagy-related genes ATG7 and BECLIN-1, enhanced conversion of LC3 I to LC3 II and decreased ratios of ILC3 I EGFP to LC3 II RFP in LC3 reporter assays. The expression levels of ATG7, BECLIN-1 and ILC3 II of TGFβ-stimulated PGC-1α knockout fibroblasts decreased compare to TGFβ stimulated wild-type fibroblasts. The ratio of ILC3 I EGFP to LC3 II RFP of TGFβ-stimulated PGC-1α knockout fibroblasts in reporter assays were comparable to unstimulated fibroblasts.
Conclusion: PGC-1α is upregulated in SSc and promotes autophagy to foster TGFβ-induced fibroblast activation. Targeting of PGC-1α prevents aberrant autophagy, inhibits fibroblast activation and tissue fibrosis.
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10. Basic and translational science in paediatric rheumatology

AB0173 ALLELIC POLYMORPHISM OF PROINFLAMMATORY CYTOKINE GENES AS A BASIS FOR THE FORMATION OF PHENOTYPES OF JUVENILE IDIOPATHIC ARTHRITIS

A. Artsymovych[1], O. Oshlianska[1], Z. Rossokha[2]. [1]*Shupyk National Medical Academy of Postgraduate Education, Paediatrics No 1, Kyiv, Ukraine;* [2]*SI "Reference-Centre for Molecular Diagnosis of Public Health Ministry of Ukraine", Kyiv, Ukraine*

Background: The pathological process of juvenile idiopathic arthritis (JIA) largely depends on pro-inflammatory cytokines, the polymorphism of the alleles of some genes of which we have the opportunity to study. No studies have been conducted on the dependence of certain features of the pathological process of JIA on the polymorphism of the IL-6(G-174C) and TNF(G308A) genes.
Objectives: To reveal the dependence of JIA phenotypes and its course on genetic polymorphism of alleles IL-6 and TNF.
Methods: Polymorphism of the IL-6 and TNF genes was studied by PCR-method using allele-specific primers 44 patients 1-17 y.o. (24f, 20m) with JIA. The level of IL-6 and TNFα in the serum was determined using ECLIA and CLIA methods.
Results: There were 73% cases with an unfavorable course of the disease (UCD) of the patients with the CC allele of the IL-6 gene, for most patients average activity was JADAS27 13.5±1.6. oJIA (50%) & uveitis (30%) were the most frequent among subgroups. The level of serum IL6 was 74.1±69.5 pg/ml, TNFα 27.4±17.3 pg/ml (ratio IL6/TNFα=4.3±2.1). Among patients with GC IL6 70% female, 79% with UCD. More often pJIA (36%, including all RF+) and eJIA (35%) were noted with the largest frequency of inclusion of the hip joints (33%), spine (35%), detection of secondary osteoporosis (43%). The metabolic changes were registered on the ECG in 82% cases. The serum IL-6 level was 11.35±2.95 pg/ml, TNF 241.75 pg/ml (IL-6/TNFα=0.047, p<0.05 vs CC allele). Children with GG IL-6 (wild allele) with a more favorable course of the JIA (31%, less than in the CC and GC groups (p<0.05), only 8% had the highest disease activity), the largest number of patients with sJIA (25%) was registered in this group. The detection of HLA B27 was significantly lower (p<0.05) than in other alleles, while 60% cases were ANA+ (more than in the group GC, p<0.05). The highest level of serum IL6 (35.3±18.9 pg/ml) & the highest average number of mutations in folate metabolism genes (4±0.51) were revealed in this group. The wild allele GG prevailed (n=32) among the TNF gene alleles, sex ratio 1:1, UCD in 70%. The number of active joints, ESR, CRP, ANA-positivity (50%), HLA B27+ (53%) were unsignificantly higher than in GA TNF allele, while serum IL6 level (22.8±9.8 pg/ml) & TNFα (12.3±4.1 pg/ml) were lower. In patients with the GA TNF gene allele, an UCD (73%), eJIA (36%) were noted slightly more often. By such parameters as the patient's gender, the presence of uveitis, damage to the hip joints, the type of synovitis, metabolic changes on the ECG, indicators were observed comparable with the wild allele group. IL6 level was 48.3±39.2 pg/ml, TNFα 636.5±420.1 pg/ml, IL6/TNFα=0.07±0.06 (vs 1.9±0.5 in GG group, p<0.05). The genotype of two wild alleles TNF GG with IL6 GG expectedly showed the smallest proportion of the UCD (33%, p <0.05), the most frequency of ANA-positivity (71%), with no uveitis and RF+pJIA in this group. All cases of RF+pJIA had TNF GA and IL6 GC. oJIA prevailed (57%) in the TNF GG&IL6 CC group, there was not a single case of sJIA, and the AJ number was the smallest (2.86±0,5). The largest group was TNF GG & IL6 GC (n=14). 91% of cases had UCD, AJ=6.6±2.4, damage to the hip joints in 40%, ESR 23.7±6.7 mm/h, CRP 14.5±5.4 mg/l, metabolic changes on the ECG in 100%, but ANA+ only at 13%. In general, there was no correlation between the cytokine content in the blood serum during of active disease in the examined children with features of allelic polymorphism of these genes.
Conclusion: Depending on the allele polymorphism of the IL-6 and TNF genes, certain phenotypes of the JIA course may be distinguished. Thus, revealing the polymorphism of these alleles in patients at the onset of the disease, we can predict to some extent its course and take this into account when choosing treatment tactics.
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AB0174 T REGULATORY CELLS LEVEL IN PERIPHERAL BLOOD OF PATIENTS WITH JUVENILE IDIOPATHIC ARTHRITIS AND ITS RELATION WITH DISEASE ACTIVITY

N. Quilis Marti[1], P. Mesa del Castillo[2], M. Andres[3,4], O. Juanola[4,5], P. Boix[4,5], R. Frances[4,5]. [1]*Hospital del Vinalopó, Elx, Spain;* [2]*Hospital Clínico Universitario Virgen de la Arrixaca, El Palmar, Spain;* [3]*Hospital general universitari d'Alacant, Alacant, Spain;* [4]*Universidad Miguel Hernández. Campus De Sant joan, Sant Joan d'Alacant, Spain;* [5]*Carlos III Health Institute, Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd), Madrid, Spain*