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In Focus

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1. Collagen-Specific T-Cell Repertoire as a New Biomarker for Rheumatoid Arthritis

HLA-DRB1 gene variants are known risk factors for several immunological diseases. Patients with rheumatoid arthritis (RA) often carry *HLA-DRB1*04* (DR4+), and have a repertoire of collagen IIp261-273-specific T cells in the peripheral blood at the onset of the disease. Gabriele Di Sante (Rome, Italy) and colleagues enrolled 90 patients with early RA to determine whether this subset of DR4-restricted collagen-specific T cells could represent new markers of severity of the disease and response to therapy. The authors examined the usage of T-cell receptor (TCR)-beta chains in peripheral blood mononuclear cells cultured with or without the human collagen II peptide p261-273. They found that the presence of T cells carrying TCR-beta chains TRBV25 and TRBV6_4 was correlated to HLA-DR and RA disease activity, and the detection of TRBV25 T cells could predict active disease in DR4+ patients. *HLA-DRB1*04/04*, *04/01* and *04/11* alleles were significantly associated with TRBV25 usage, higher disease activity at RA onset, and poor response to disease-modifying anti-rheumatic drugs. The findings could help predict the course of RA and tailor treatments for RA patients.

2. Exposure to BCG Leads to NK Cell Priming for Better Recognition of Bladder Cancer Cells

The tuberculosis vaccine Bacillus Calmette-Guérin (BCG) is used as intravesical immunotherapy to treat non-muscle-invasive bladder cancer and help prevent recurrence. To test how BCG may interact with bladder cancer cells and natural killer (NK) cells, Eva M. García-Cuesta, Gloria Esteso and collaborators (Madrid, Spain) incubated peripheral blood mononuclear cells from healthy donors with BCG, and analyzed changes in NK cell phenotype and cytotoxic function against several bladder cancer cell lines. Incubation with BCG resulted in vigorous proliferation of $CD56^{bright}$ NK cells that initially produced IFNγ in response to bladder cancer cells and later made cytotoxic responses. The researchers also analyzed soluble factors in the urine of bladder cancer patients treated with BCG or mitomycin and showed that the cytokines present in urine of BCG-treated patients belonged to an 'innate-immune' type of response. The authors concluded that BCG can activate NK cells and promote a better recognition of bladder cancer cells.

3. Role of Ets-2 and FoxP3 in Multiple Sclerosis Pathogenesis

Multiple sclerosis (MS) is characterized by autoimmune myelin damage, in which pathogenic Th1 and Th17 cells may play a role. Ets-2 and FoxP3 are transcriptional silencers of naive Th effectors (Teffs) and Tregs, and they suppress cytokine gene expression by binding to *ARRE-2* promoter element. In this study, Ioannis Panagoulias (Patras, Greece) and colleagues analyzed the expression of Ets-2 and FoxP3 in Th cells isolated from MS patients and age/sex-matched healthy controls. The authors found that the median % of activated Teffs and Tregs were 2.89 and 0.56 in the acute phase of MS, and 0.8 and 2.37 in remission phase (vs 0.04 and 2.87 in controls). In MS patients, Teffs and Tregs showed very low levels of Ets-2 and FoxP3 synthesis and immunopositivity in the nucleus; ChIP analysis also revealed no Ets-2 binding and very weak FoxP3 binding to *ARRE-2* (vs controls). Significantly higher expression of IL-2 and IL-17A in naive Teffs, TNFα in memory Teffs, and IL-2 and IFNγ in Tregs were also seen in MS patients. The authors concluded that low-level synthesis and dysfunction of Ets-2 and FoxP3 in Th cells of MS patients are probably responsible for the increase in pathological Th1 and Th17 cell clones, leading to MS pathogenesis.

4. *DARC* Gene Polymorphism Associated with Total Joint Replacement Failure

Prosthesis failure is not uncommon in patients with total joint replacement (TJR), with unknown genetic risk factors. Petra Schneiderova (Olomouc, Czech Republic) and collaborators divided 354 TJR patients into those with complications (either aseptic loosening [AL, n = 110]; or prosthetic joint infection [PJI, n = 126]) and control group without complications for at least 10 years (n = 118). The authors genotyped 11 single nucleotide polymorphisms (SNPs) that are known to affect serum levels of several pro-inflammatory molecules (IL-6, CCL2/MCP-1, and CRP) and erythrocyte sedimentation rate (ESR). They found only one SNP, *rs12075*G* allele, which was present more frequently in patients with complications (46.6%) compared to those without complications (36.0%, p = 0.007, OR = 1.55, 95% CI = 1.13–2.14). This allele was found more in patients with AL (49.5%), and less so in patients with PJI (44.0%). *rs12075* is located in the gene *DARC* (Duffy antigen receptor for chemokines). This study suggested the allele *rs12075*G*, which is linked to lower serum levels of CCL2/MCP-1, as a genetic risk factor for prosthesis failure (especially AL).

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5. Hsp72 as a Potential Autoantigen in Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF) is a poorly understood interstitial lung disease. In this study, Ross Mills (Edinburgh, UK) and colleagues aimed to elucidate the role of the recently identified heat shock protein 72 (Hsp72) in IPF pathogenesis. They screened for Hsp72 and anti-Hsp72 antibodies in the serum and brochoalveolar lavage fluid (BALF) of IPF patients. Significantly higher concentration of Hsp72 was found in the serum of IPF patients compared to controls ($p \leq 0.0001$), with no difference in BALF ($p = 0.0577$). Using ELISA, the research group found no significant difference in anti-Hsp72 antibodies in the serum of IPF patients compared to controls ($p = 0.8286$). However, they found a significantly higher concentration of anti-Hsp72 antibodies in the BALF of patients compared to controls ($p \leq 0.0001$), with a significant difference between progressors and non-progressors among IPF patients ($p = 0.0080$), suggesting a possible role in outcome prognosis by measuring BALF anti-Hsp72 antibodies. The findings further support the hypothesis that Hsp72 dysregulation may be involved in IPF pathogenesis.