ACUTE CARDIOVASCULAR EVENTS RISK IN RHEUMATOID ARTHRITIS PATIENTS TREATED WITH TOFACITINIB OR TNF INHIBITORS, A NATIONWIDE COHORT STUDY: RELATION STUDY

Keywords: Rheumatoid arthritis, Targeted synthetic drugs, Real-world evidence

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Background: Patients with IMID, and notably patients with rheumatoid arthritis (RA), are at increased risk of major adverse cardiovascular event (MACE) compared with the general population [1,2]. It is hence paramount to assess the impact of biological or targeted DMARD (e.g., tofacitinib and TNFi) on the risk of MACE in patients already at-risk, particularly in the context of ORAL Surveillance which showed a higher risk MACE with tofacitinib, in comparison with TNFi, in patients treated in real-world settings. Studies with longer follow-up durations may be necessary to understand the long-term implications of tofacitinib vs TNFi on the risk of MACE.

References: NIL.

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SURVIVIN REGULATES T CELL RESPONSES THROUGH DEPOSITION OF HISTONE H3 MARKS AND MODULATES RESPONSE TO TREATMENT WITH JAK-INHIBITORS

Keywords: Targeted synthetic drugs, Adaptive immunity, Rheumatoid arthritis

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Background: Multiple genetic polymorphisms are associated with high risk for rheumatoid arthritis (RA) [1]. The importance of epigenetic processes has been postulated, but precise molecular mechanisms behind these associations remain largely unexplored. Survivin is an important player in RA, which has recently been shown essential for IFN signaling in CD4 T lymphocytes acting in partnership with IRF1 [2].

Objectives: We study how survivin-dependent epigenetic depression of histone H3k9ac in RA risk loci affects function of CD4 T cells and response to JAK inhibition.

Methods: Chromatin of CD4+ cells (n=12) was immunoprecipitated with antibodies to histone H3K27ac, H3K4me3, and survivin, and sequenced (ChIP-seq, Illumina). Parallel ChIP-seq and RNA-seq was done in CD4+ cells treated with survivin inhibitor YM155. Peaks with change >30% in deposition of H3K27ac and/or H3K4me3 upon YM155-treatment were annotated to the genomic regulatory elements (RE) via GeneHancer database. Single nucleotide polymorphism (SNP) related to RA risk were identified within those RE. CD4+ T cell transcriptomics by RNA-seq was done in 24 random RA patients and in 59 RA patients treated with MTX (n=18), TNFi (n=10), JAKi (n=24) and having no DMARDs (n=7). The genes differentially expressed (DEG, nominal p<0.05) in IRF1 and/or H3K27ac upregulated in JAKi-treated RA were identified by DESeq2 (R-studio, Bioconductor).

Results: Deposition of 15% (1705/11512) of H3K4me3 and 17% (1943/11530) of H3K27ac peaks changed >30% upon survivin-inhibition. Approximately 50% of these peaks overlapped with survivin peaks. The change in H3K4me3 peaks was significantly larger if the peak colocalized with survivin peak. These peaks were located within 228 RE, 28 of these RE contained 52 RA risk SNPs. Among others, changeable peaks were accumulated within ICOS/CTLA4/CD28 locus and contained 7 SNPs. Majority of genes connected to the SNP-containing RE (110/153 genes) were transcriptionally different in IRF5/CD4+T cells and participated in the regulation of immune system (GO:0002682, FDR=4.3e-4), regulation of IL2 production (GO:0032863, FDR=0.012), TNF mediated signaling (GO:0033209, FDR=5.4e-3). These SNP-RE connected genes formed three independent clusters 1) TCR receptor co-stimulators (CD40, ICOS, CTLA4, CD28, CD244, TRAF6 and TBX21, SLAMF1, TNFRSF9), 2) connected to the LCK interacting transmembrane adapter 1 (LIME1, SLC2A4RG, ZGPAT, GMEB2, TNFRSF6B, RET1L3) and 3) heat-shock proteins (HSPD1, HSP90A1, HDAC7, KPNB1). The clusters were functionally connected to survivin partners IRF1 and SMAD3. Notably, transcription of IRF1 and JAK4 in CD4+ T cells was significantly changed (all, nominal p<0.05) in CD4+ cells upon survivin inhibition by YM155. Since survivin mediates IFN-dep-endent processes [2], we analyzed transcription of 110 SNP-RE connected DEG in CD4+ cells of JAKI-treated RA patients. We found that DEG in IRF1 and SMAD3 clusters were inversely affected by JAK, e.g., IRF1-related CD28, ICOS, and SLAMF1 upregulated after survivin inhibition were suppressed.