РАЗДЕЛ I

БИОИНФОРМАТИКА

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IDENTIFICATION OF POTENTIAL MASTER REGULATOR MOLECULES RESPONSIBLE FOR NON-TOLERANT REACTION IN CHRONIC INFLAMMATORY DISEASE *

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Abstract

Chronic inflammatory diseases like atherosclerosis and CVD significantly impact global health by causing immune-mediated organ damage. This study aims to identify potential biomarkers of immune cell populations driving chronic inflammation. We performed transcriptomic analysis of 82 samples and identified OSMR and TREM2 as key downregulated genes, suggesting their potential as searched biomarkers.

Motivation and Aim

Chronic inflammatory diseases, including atherosclerosis, cardiovascular disease (CVD), rheumatoid arthritis, and inflammatory bowel disease, significantly impact global health. These diseases arise when the immune system shows inadequate response to endogenous stimuli, leading to organ damage and dysfunction. Despite extensive research on the molecular and cellular mechanisms of chronic inflammation, identifying immune cell populations that initiate and drive this process early remains challenging. This study aims to identify biomarkers that can highlight those populations and suggest mechanisms behind the development of chronic inflammation. By discovering these molecules, we hope to gain insights into the signaling pathways and cellular processes involved, laying the foundation for early diagnostics and precision medicine for patients with chronic inflammatory diseases.

Methods and Algorithms

We fused ρ0 THP-1 cells with thrombocytes of atherosclerotic patients, then stimulated resulting cybrids with LPS and measured IL1b, IL6, IL8, and CCL2 levels. We also performed RNA sequencing of 82 RNA samples before stimulation using Illumina MiSeq. Reads were mapped to the human GRCh38 assembly (Ensembl) using STAR. The count matrix was generated within the STAR protocol, followed by differential expression analysis with DESeq2 v1.44.0 ($-0.6 < \log2FC < 0.6$ and p-value < 0.05).

Results

We conducted experiments on 13 monocyte cybrid lines and a control THP-1 line to measure cytokine secretion levels (IL1B, IL6, IL8, and CCL2) before and after LPS stimulation. Cybrid lines were classified into three groups based on their immune response for each cytokine (tolerant, non-tolerant, and non-responder). IL6 and IL1B secretion patterns were similar, resulting in equivalent subsequent analysis outcomes for these groups. RNA sequencing was performed on untreated samples, and DESeq2 was used for differential expression analysis for each cytokine group, considering genes as significantly differentially expressed with $|\log2FoldChange| > 0.6$ and p-value < 0.05 (see Table).

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DGE with grouping by cytokines (non-tolerant vs tolerant)

Cytokine group	Upregulated	Downregulated
IL6 | IL1b	184	512
IL8	6	61
CCL2	18	379

Our analysis identified OSMR and TREM2 as downregulated in the IL6, IL1B, and CCL2 groups. TREM2 suppresses PI3K and NF-kappa-B signaling in response to lipopolysaccharides, promoting phagocytosis, reducing pro-inflammatory cytokine and nitric oxide production, inhibiting apoptosis, and increasing IL10 and TGFB expression. During oxidative stress, TREM2 enhances anti-apoptotic NF-kappa-B and ERK signaling. Given its good coverage in our analysis, TREM2 is a strong candidate for further investigation as a key regulatory factor in chronic inflammation and a potential biomarker.

OSMR, part of the IL6R receptor family, interacts with STAT family proteins, which are transcription activators, and is upregulated by bacterial lipopolysaccharides (LPS). Although OSMR coverage was limited, suggesting possible false positives, its consistent downregulation indicates the need for further validation. Interestingly, the OSM gene was previously highlighted in our publication as one of the MRs in chronic inflammation [1], and now we have identified differential expression of its receptor, reinforcing its relevance.

Conclusion. In summary, TREM2 and OSMR could serve as biomarkers for identifying specific monocyte populations involved in chronic inflammatory responses. Further validation and exploration of these findings are necessary to fully understand their roles and therapeutic potential.

References

1. Sukhorukov N. V., Khotina V. A., Borodko D. D. et al. Evidence for the involvement of gene regulation of inflammatory molecules in the accumulation of intracellular cholesterol: the mechanism of foam cell formation in atherosclerosis // Current Medicinal Chemistry. 2024. Vol. 31. P. e190224227147.