

Conclusion: In addition to inducing p75NTR up-regulation, inflammatory stimuli increase the release of proNGF in arthritis SFs. Autocrine proNGF binds to p75NTR and further enhances pro-inflammatory cytokine production, creating a vicious circle that amplifies the inflammatory response. Blocking the binding of endogenous proNGF to its receptor p75NTR strongly reduces the production of inflammatory mediators and prospects the use of p75NTR inhibitors as a new therapeutic approach to chronic arthritis.

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AB0063

A SYSTEMS APPROACH TO INVESTIGATE INFLAMMATION RESOLUTION BY MULTICOMPONENT MEDICINAL PRODUCT TR14

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Background: Acute inflammation is a nonlinear, spatio-temporal process for the removal of invading pathogens and the repair of damaged tissues to re-establish homeostasis. If not resolved, it leads to chronic inflammatory clinical phenotypes. The current medical paradigm is based on using single-molecule inhibitors aiming to block certain molecular pathways involved in inflammation. Complex diseases, where large numbers of feedback mechanisms play a central role, require multi-target interventions [1]. Dynamics of feedback mechanisms associated with multiple therapeutic checkpoints require systems biology approaches.

Objectives: The objective of our study was to construct a comprehensive molecular interaction map (MIM) of acute inflammation and its resolution. We further aimed to understand the effect of Traumeel (Tr14), a multicomponent drug, on inflammation resolution, by mapping previously published Tr14 transcriptomics data [2] from a wound healing murine model onto the MIM.

Methods: We constructed a comprehensive MIM using damage-, and pathogen-associated molecular patterns (DAMPs and PAMPs) and established disease genes from selected acute inflammatory clinical phenotypes as seed molecules. From the MIM, we identified feedback loops (FBLs) with the NetDS Cytoscape plugin using our previously published methodology [1]. All FBLs were merged to create a core regulatory network responsible for the overall dynamics of acute inflammation initiation, transition and resolution.

Using Tr14 transcriptomics data to identify acute inflammatory processes enriched at various time points, we combined RPKM values of each individual splice variant into the parent gene using the RSEM method [3]. The expression profile of whole genes was favored due to the lack of splice variant-specific ontology data. Further, the fold change expression profile for each gene was calculated by comparing Tr14-treated vs untreated mice. These data were mapped to the core regulatory network, and time point-specific sub-networks were identified by keeping nodes with absolute fold change expression of ≥ 1.5 and a p-value ≤ 0.05 . Furthermore, we identified enriched immune-related processes regulated by Tr14 at each time point using the Cytoscape ClueGo app.

Results: The MIM has, as of January 2019, 3300 interactions, which are divided into 24 functional modules based on acute inflammation-related gene ontology terms. From the MIM, we identified 435 FBLs which were merged to extract a core regulatory network. After mapping of Tr14 gene expression fold change data at time points 12h, 24h, 36h, 72h, 96h, 120h and 192h, we identified that large numbers of FBLs were differentially regulated at early time points. This number decreased substantially at later time points. At time point 192h, we could identify only 6 differentially regulated nodes with no specific role in immune regulation, indicating that the inflammation was resolved mostly before 192h after injury. Combined expression profile of all the genes associated with the "increase acute inflammation" ontology showed an approximately 24hrs shift towards faster resolution in Tr14-treated mice.

Conclusion: Molecular interaction maps facilitate gene expression data analysis to identify enriched molecular processes and cell/tissue specific-phenotypes. Tr14-induced gene expression changes can be linked to inflammation-related

biological functions as defined by enriched GO terms. Our analyses suggest that Tr14 modulates multiple network components at early time points, which can be linked to inflammation resolution.

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SERUM TENASCIN-C LEVELS ARE ELEVATED IN PATIENTS WITH AXIAL SPONDYLOARTHRITIS

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Background: Tenascin-C (TNC) is a pro-inflammatory extracellular matrix glycoprotein that is synthesized in various pathological conditions. TNC induces inflammatory activity and promotes damage of joints. Its expression in adults is restricted to sites of tissue injury, particularly during phases of inflammation and active tissue remodelling. Only a few studies have described elevated serum TNC levels in ankylosing spondylitis (AS) compared to healthy controls (HC).

Objectives: The aim of this study was to examine the levels of serum TNC among different axial spondyloarthritis (axSpA) subsets and whether TNC levels are related to disease activity measures or other clinical features.

Methods: Sixty-one patients who fulfilled the Assessment of SpondyloArthritis international Society (ASAS) classification criteria for axSpA and twenty age and sex-matched HC were included in this study. Based on imaging, patients were further classified as AS (n = 45) and as nr-axSpA (n = 16). Patients with AS were further divided into two subsets based on the absence (n=22) or presence of syndesmophytes (n=23).

TNC serum levels were determined using ELISA. The following data were collected: clinical and laboratory disease activity measures; demographic status; disease-related factors such as the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and CRP levels. Statistical analyses were performed with GraphPad Prism 5.1. The data are presented as the median and interquartile range.

Results: TNC serum levels were elevated in axSpA patients (535.3 (457.7-677.2) ng/mL) compared to HC (432.1 (329.1-565.9) ng/mL, p= 0.007). Dividing axSpA into nr-axSpA and AS subsets the difference was observed only between AS patients and HC (535.3 (434.5-677.2) vs. 432.1 (329.1-565.9) ng/mL, p=0.022). TNC serum levels did not correlate with disease activity biomarkers (serum CRP or BASDAI) in patients with axSpA. Although we have not observed correlation between TNC and mSASSS radiographic score, weak correlation with disease subsets was found (r=0.25, p=0.025).

Conclusion: We demonstrated here elevated serum TNC levels in patients with axSpA, particularly in those with syndesmophytes, which may suggest its role in bone formation during radiographic stage of the disease.

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