RESPONSE TO DMARDS AND TNFI THERAPIES

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Background: The clinical outcome of the most common therapeutic options of rheumatoid arthritis (RA) patients, such as conventional disease-modifying antirheumatic drugs (DMARDs) and TNF inhibitors (TNFI) is still unpredictable, since a high percentage of RA patients inadequately responding to TNFi, prior therapy is associated with a poor clinical outcome. These data were similarly observed in patients before receiving DMARDs, where a signature of upregulated chemokines and pro-inflammatory mediators characterised a cluster with a high percentage of non-responder patients.

Conclusion: A pro-inflammatory signature, where chemokines are predominately upregulated, prior to the serum of RA patients before therapy, is associated with a poor clinical outcome. This newly identified signature, which deserves a more in-depth analysis, might be clinically useful guiding precision medicine and novel therapeutic approaches.

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THE ANALYSIS OF THE INFLAMMATORY PROTEOME IN RHEUMATOID ARTHRITIS IDENTIFIES COMMON SIGNATURES ASSOCIATED WITH THE CLINICAL RESPONSE TO DMARDS AND TNFI THERAPIES

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Background: Tyrosine kinases receptors MerTK and Axl have been implicated in the pathogenesis of several autoimmune diseases. Despite sharing significant structural homology and having common ligands, Axl and MerTK have distinct features and biological functions [1]. A growing body of evidence suggests that both Axl and MerTK play a crucial role in Rheumatoid Arthritis (RA) pathogenesis and progression and may be exploited as novel therapeutic targets. [2]. However, numerous unanswered questions remain to be addressed.

OBJECTIVES:

i. To define common and distinct gene-partners of Axl/MerTK and quantify their expression in RA synovial tissue.

ii. To assess the co-expression of Axl/MerTK by synovial cells.

iii. To outline the longitudinal variation in Axl/MerTK expression upon treatment intervention.

Methods: Synovial tissue samples were collected by US-guided biopsy from: i. Patients with early (<12 months) RA DMARDs/steroid-naïve (n=87); and ii. RA patients who failed the first-line biologic with TNF-inhibitors (TNFI) before and 16 weeks after receiving either Rituximab (RTX) or Tocilizumab (TOC) (n=164) [3]. Gene expression was obtained by bulk RNAseq performed on an Illumina HiSeq2500 platform. Axl/MerTK-modules were defined using STRING networks and the module expression determined by the mean z-score of regularized log transformed expression for all genes in the set. Axl, MerTK, CD55, CD90, CD68 protein expression was analysed by immunofluorescence staining.

Results: Using STRING network analysis, we defined an Axl- and a MerTK-module composed of 31 predicted gene-partners of either Axl or MerTK. Thirteen genes were common to both modules and included the ligands Gas6 and ProteinS, and EGFR. Conversely, eighteen genes were uniquely present in the Axl-module (e.g., PIK3-family, IFIR1, IFNAR1 and STAT3) or the MerTK-module (e.g., Galectin3 and TULP). Recently discovered MerTK ligands, FCGR1A/CD64, PTPN1 and MEGF10). Axl/MerTK-modules quantified in the early-arthritis treatment-naïve RNAseq dataset showed a significant negative correlation with the synovitis score (Axl r=-0.33, p=0.0032; MerTK r=-0.30, p=0.0034). Moreover, CD68-macrophages of the Lining showed notable heterogeneity between patients: they could express either Axl or MerTK alone, or co-express both. Axl was also present in most CD55+ Lining Fibroblast-Like Cells (FLS) but not by CD90+ Sublining FLS while MerTK, as expected, was restricted to macrophages, including intra-aggregate tangible-body-macrophages. To define how Axl and MerTK vary depending on disease stage and treatment exposure, we quantified their gene expression in active RA patients inadequately responding to TNFi, prior and 16 weeks after starting second-line biologic (RTX or TOC) [3]. Differently from the early-arthritis cohort, MerTK was significantly up-regulated in synovia characterised by higher degree of tissue inflammation (lympho-myoidel > diffuse-myoidel > pauci-immune, p<0.0001) and significantly positively correlated with several cytokines’ genes such as TNF, IL-6, CCL8 and IL-10. MerTK expression was dependent on clinical response to RTX, but not TOC, as assessed by EULAR response (DAS28CRP, good vs none/mod, FDR Resp 0.048). Conversely, Axl expression compared with Cluster 2 (C2), where a signature of 16 chemokines was significantly enriched (CCL3 - 3, -10, -20, -23, CXCL1, CXCL10, -4, -5, -6, -9; MCP-1, -3, -4). Clinically, 25% of the non-responders’ patients was included in C2, while 75% was located in C1, suggesting that a prominent circulating chemokines profile prior therapy is associated with a poor clinical outcome. These data were similarly observed in patients before receiving DMARDs, where a signature of upregulated chemokines and pro-inflammatory mediators characterised a cluster with a high percentage of non-responder patients.