CXCL17 IN RHEUMATOID ARTHRITIS: INTERFERONE-ANTI-INFLAMMATORY EFFECTS OF SPLEEN TYROSINE KINASE (SYK) INHIBITOR, PICEATANNOL, ON FIBROBLAST-LIKE SYNOVIOMETABOLISM IN RHEUMATOID ARTHRITIS

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Background: CXCL17 is the latest chemokine discovered and was reported to influence angiogenesis and monocyte trafficking1,2. Its role in rheumatoid arthritis (RA) has not been assessed so far.

Objectives: To assess the role of CXCL17 and its putative receptor G-protein-coupled receptor 35 (GPR35) in RA.

Methods: Synovial tissue from joint replacements of RA and osteoarthritis (OA) patients was used for CXCL17 and GPR35 immunohistochemistry and in-situ hybridization/immunofluorescence double-stainings. CXCL17 concentration in the synovial fluid of RA and CXCL17 production by synovial fibroblasts and smooth muscle cells after stimulation with TNF-α, INF-γ and IL-1β was quantified by qPCR and ELISA. Angiogenesis was assessed by a human umbilical vein endothelial cell assay.

Results: CXCL17 and GPR35 are widely expressed in the synovial membrane of RA compared to OA (p<0.006). Within the synovial membrane CXCL17-mRNA could be located to vascular smooth muscle cells. INF-γ significantly induced CXCL17-mRNA and protein production in RA synovial fibroblasts (1.88-fold, p=0.019 and 2-fold, p=0.002 respectively) and rat smooth muscle cells (67-fold, p=0.02 and 3.7-fold, p=0.001). CXCL17 was detected in the synovial fluid of RA (mean 310 pg/ml). In vitro angiogenesis was inhibited by CXCL17. This effect was reversed by specific GPR35 antagonists.

Conclusion: CXCL17 is abundant in RA synovial tissue, localizes to vascular smooth muscle cells and fibroblasts, and is inducible by INF-γ. Antiangiogenic properties are mediated by GPR35. CXCL17 and GPR35 may constitute a hitherto unrecognized regulatory protein in RA pathogenesis and therefore be interesting drug targets.

REFERENCES


Disclosure of Interests: None declared


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VERY STRONGLY POSITIVE RHEUMATOID FACTOR LEVELS (10-FOLD HIGHER THAN THE UPPER NORMAL RANGE) RATHER THAN “RHEUMATOID FACTOR POSITIVITY” PER SE ARE ASSOCIATED WITH SMOKING IN FEMALE RA PATIENTS WITHOUT A HISTORY OF OCCUPATIONAL DUST AND FUME EXPOSURE

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Background: Rheumatoid factor (RF) forms part of the 2010 EULAR/ACR classification criteria. A weakly positive RF is defined as up to 3-fold higher and a strongly positive RF >3-fold higher than the upper normal range.

Methods: RF levels at least 4-fold higher than the upper normal range of normal had an adjusted hazard ratio for RA development of 20 (95% CI 15 to 46) compared to only 6.3 (4.1 to 10) for individuals with levels 2 to 4-fold above the upper normal range.

We have recently reported median RFs of greater than 10-fold higher than the upper normal range in nodular RA which is far more prevalent in smokers than non-nodular RA. We have arbitrarily defined this level of RF as very strongly positive as it defines a disease subtype.

Additionally, RF levels are strongly associated with additive exposures to both smoking and industrial vapours, gases, dust and fumes (VGDF) in male RA, with only 8% having been exposed to neither VGDF nor cigarette smoke.

Objectives: Accordingly, we have studied female RA in whom VGDF exposures are less common to compare RF levels in an appreciable number of smokers and non-smokers without the significant confounding effect of VGDF exposures to determine if smoking is specifically associated with a very strongly positive RF.

Methods: Medical record analysis yielded 241 female RA patients seen in clinic between January and June 2018 without exposures to industrial VGDF. These patients were stratified for a history of smoking. RF was measured with Tina-quant Rheumatoid Factors II Test System, by Roche Diagnostics Corporation at the time of RA diagnosis. A value of <14 IU/ml was considered as negative as per manufacturer guidelines, a RF weakly positive (14-42 IU/ml), RF strongly positive (42-140 IU/ml) and RF very strongly positive (>140 IU/ml).

Results: There were 109 never smokers and 132 smokers with a median RF of 21 IU/ml and 53 IU/ml respectively, p<0.05. In never-smokers significantly more were seronegative 46/109 (42%) vs. 32/132 smokers (24%), odds ratio (OR)=2.22 (95% confidence interval (CI) 1.28-3.83, P=0.004). Of never smokers 22/109 (20%) were weakly RF positive and very similar to smokers 28/132 (21%).29/109 (27%) of never smokers were strongly RF positive and a similar proportion of smokers 37/132 (28%) were strongly RF positive. Finally in never smokers, only 12/109 (11%) very strongly RF positive compared to 35/132 (27%) of smokers, OR=2.89 (95% CI 1.41-5.89, p=0.004).

Conclusion: Considering female RA smokers and non-smokers, the difference in RF positivity was exclusively accounted for by an increased prevalence of a very strongly positive RF in female smokers. This suggests that smoking has an impact on very strongly positive RF levels rather than RF positivity per se without the important confounding factor of VGDF exposure.

REFERENCES


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