contain significantly more IgD⁺CD95⁺ germinal center B cells ($P < 0.01$) with a higher expression of the costimulatory molecules CD80 and CD86 compared to WT. The vertebrae also contained more CXCR5⁺PD-1⁺FoxP3⁺CTLA4⁺ T regulatory cells and a trend towards an increase in CXCR5⁺PD-1⁺FoxP3⁺CTLA4⁺ T follicular helper cells in tmTNF tg mice. Meanwhile, B cell development in the BM of tmTNF tg hind limbs was not altered. Furthermore, BM, spleen and vertebrae from tmTNF tg mice contained significantly more IgA⁺ plasma cells compared to WT littermates. Of note, tmTNF tgxTNF-RI^{-/-} mice did not display lymphoid aggregates or HEVs in the BM, while tmTNF tgxTNF-RII^{-/-} mice did, although to a lesser extent than tmTNF tg mice.

Conclusion: tmTNF overexpression in mice results in extensive lymphoid aggregates in the BM that are often organized in ELS, which may be mediated via TNF-RI signaling. These ELS might result in an increase of IgA⁺ plasma cells in tmTNF tg mice. Ongoing studies will look further into this and may indicate whether these findings contribute to the pathology observed in these mice.

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FRI0368 VASCULAR CALCIFICATION BY INFLAMMATION COULD BE AN IMPORTANT CAUSE OF CARDIOVASCULAR DISEASE IN PATIENTS WITH ANKYLOSING SPONDYLITIS

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Background: Patients with ankylosing spondylitis (AS) have a higher risk of cardiovascular disease. Atherosclerosis is a main pathological process of cardiovascular disease and calcified plaque is a characteristic feature of atherosclerosis. Inflammation plays a potential role in vascular calcification. There is no previous study revealing the mechanism of vascular calcification in AS.

Objectives: We investigated the relationship between vascular calcification and inflammation in patients with AS.

Methods: Sixteen male patients aged over 20 years with AS were enrolled. They fulfilled the modified New York criteria and each of their ankylosing spondylitis disease activity score was more than 2.1. Sex and age matched nine healthy controls were also recruited. Mouse MOVAS (American Type Culture Collection, ATCC[®], CRL-2797TM) vascular smooth muscle cells were stabilized in maintenance medium for 24 hours. Then the amount of serum equivalent to 10% of maintenance medium from subjects was added and cells were stimulated for another 72 hours. We exchanged this medium with calcification medium every third day and cells were cultured for another 11 days. After 2 weeks, cells were stained with Alizarin Red S and the optical density (OD) was measured while being compensated by cell viability. For Western blotting, cells were stabilized for 24 hours and stimulated for another 72 hours through the same procedure as that of Alizarin Red S staining. Then we measured the level of protein expression in PPAR-gamma, beta-catenin, TNF- α , interleukin (IL)-23, and MMP7.

Results: The level of OD of MOVAS cells treated with serum from AS patients (19.503 ± 6.422 , mean $\pm$ SD) was significantly higher than that from controls (12.724 ± 5.746) ($P=0.027$, Mann-Whitney test). The level of MMP7 expression of MOVAS cells treated with serum from AS patients (1.921 ± 0.702) was significantly higher than that from controls (0.779 ± 0.191) ($P=0.000$, Mann-Whitney test). The level of beta-catenin expression of MOVAS cells treated with serum from AS patients (1.292 ± 0.356) was significantly higher than that from controls (0.887 ± 0.310) ($P=0.025$). There was negative correlation between PPAR-gamma and TNF- α ($\rho=-0.762$, $p=0.028$, Spearman rank correlation coefficient), and between PPAR-gamma and IL-23 ($\rho=-0.601$, $p=0.039$); positive correlation between MMP7 and TNF- α ($\rho=0.833$, $p=0.010$), and between MMP7 and IL-23 ($\rho=0.797$, $p=0.002$).

Conclusion:

1. Serum from AS patients showed increased calcification of vascular smooth muscle cells than serum from controls.
2. The level of vascular calcification marker from vascular smooth muscle cells treated with serum from AS patients was significantly higher than that from controls.
3. There were negative relationship between inflammatory markers and inhibitory marker of vascular calcification but positive relationship between inflammatory markers and stimulatory marker of vascular calcification.

These findings suggest that vascular calcification by inflammation could be an important cause of cardiovascular disease in AS patients.

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FRI0369 TOWARDS MORE PRECISE ESTIMATES OF THE FAMILIAL AGGREGATION AND HERITABILITY OF ANKYLOSING SPONDYLITIS – A SWEDISH NESTED CASE-CONTROL STUDY

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Background: Ankylosing spondylitis (AS) is known to have strong familial aggregation, but studies quantifying the familial risk are few and have reached varying results. Familial risks reported from population-based studies range from 17 to 94 in first-degree relatives of AS cases.^{1,2} The heritability (i.e., the proportion of variance in AS liability explained by genetic variation) has been reported to >90%, based on very small studies of twins.³

Objectives: To assess the familial aggregation and heritability of AS among all Swedish AS patients, and to investigate if risks vary by type of first-degree relative or sex.

Methods: We identified all patients with an ICD-10 code of AS in the Swedish National Patient Register (NPR) between 1 January 2001 and 31 December 2016. To increase validity, index patients were required to have two or more visits listing an AS diagnosis, and at least one of the visits being to a specialist in rheumatology or internal medicine. Each index patient was matched on sex and birth year to 50 general population controls from the Total Population Register. First-degree relatives of index patients and controls were identified through the Multi-generation register. Their disease status was ascertained from the NPR in a similar manner as for index patients. Familial risks of AS among first-degree relatives were calculated as odds ratios (ORs) with conditional logistic regression. Based on the familial risks, the corresponding heritability was calculated for a range of plausible prevalence estimates.

Results: We identified 13 795 patients that met the inclusion criteria. Of their siblings, parents, and children, 3.6, 2.3, and 2.1% respectively also had AS. The overall familial OR when having one affected relative was 19.4 (95% CI 18.1-20.8). The estimates were similar for relatives of different kinds (see table), but having more than one affected relative resulted in a higher risk (OR 68.0 (95% CI 51.3-90.1)). Heritability, estimated from sibling risk, was 77%. There were no clear-cut differences between the sexes, but women tended to have an elevated familial risk if the affected relative was female, and slightly lower heritability compared to males. These estimates can be considered as an upper limit of heritability, as shared environmental factors have not been taken into account in calculations.

Conclusion: Familial risks of AS were similar between different types of first-degree relatives, and no significant gender difference was seen on the heritability scale. Although high compared to most other diseases, the familial risks and heritability were lower than previous reports from other countries, though in line with earlier Swedish findings using in part the same data source. The heritability proposed here might still be an overestimate of the true influence of genetics on disease risk. Thus, efforts should also be directed at identifying other risk factors for AS that are not of genetic origin.

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