

Semaphorin 4D induces an imbalance of Th17/Treg cells by activating the aryl hydrocarbon receptor in ankylosing spondylitis

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Abstract

Objectives: to investigate the mechanism by which Sema4D affects the pathogenic progress of ankylosing spondylitis (AS). **Methods:** Soluble Sema4D (sSema4D) levels in serum were analyzed by enzyme-linked immunosorbent assay. The cell surface levels and transcripts of Sema4D were evaluated in CD4+ and CD19+ cells from the AS patients and healthy individuals. The mRNA expression levels were assessed by quantitative polymerase chain reaction (qPCR). The proportions of Treg cells and IL-17-producing T-cells (Th17 cells) differentiated from CD4+ T cells were analyzed by flow cytometric analysis. The aryl hydrocarbon receptor (AhR) agonistic effect of Sema4D was detected by analyzing the activation of downstream signaling pathways and target genes using Luciferase and EROD assay. **Results:** Levels of sSema4D were elevated in both serum from AS patients, and clinical features markers were correlated with serum sSema4D levels. Sema4D facilitated CD4+ T cells proliferation and Th17 cells differentiation and inhibited Treg cells differentiation by enhancing ROR γ t expression and reducing Foxp3 expression, with increasing expression and secretion of IL-17 and IL-22. It induced the expression and activity of AhR target gene CYP1A1 and XRE reporter activity via interaction with CD72. **Conclusions:** These findings indicate that Sema4D as a potent activator of T cells in the immune response contributes to the inflammation of AS by inducing imbalance in Th17 and Treg cell populations in an AhR-dependent manner, suggesting it is a crucial participant in AS pathogenesis.

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Table 1: Baseline characteristics of study population

Characteristics	AS (n=56)	HC (n=43)	<i>p</i> value
Age (yrs old)	35.24±13.37	32.36±12.37	NS
Male/female	42/14	30/13	NS
Disease duration (yr)	14.2± 9.7		
Axial with peripheral arthritis/axial disease only (patient number)	33/23		
HLA-B27 (+) (%)	52 (92.8%)		
CRP (mg/dl)	23.2±12.5		
ESR (mm/h)	24.9±15.3		
BASDAI	5.2±3.4		
Schober's test (cm)	3.56±2.18		
Finger to floor (cm)	17.8±14.9		
Chest expansion (cm)	4.47±1.56		
Right lateral bending (cm)	8.32±4.26		
Left lateral bending (cm)	8.58±7.13		
Occipital to wall (cm)	4.23±6.57		
Tragus to wall (cm)	12.5±6.24		
Intramalleolar distance (cm)	93.22±20.15		
Cervical spine lateral rotation, right (degree)	43.4±29.8		
Cervical spine lateral rotation, left (degree)	46.8±27.3		