spondylitis (SA) are associated with an increased cardiovascular (CV) mortality. Quantitative abnormalities in lipid profiles are insufficient to explain this excess of CV risk and a qualitative approach of HDL composition is required to identify loss of atheroprotective functions and to correctly identify patients at risk. Atheroprotective functions of HDL are directly linked to the structure of HDL mainly composed of phospholipids (PL).

Objectives: The main objective of this study is to analyze the PL composition of HDL in patients with chronic inflammatory rheumatic diseases and to compare to matched healthy controls.

Methods: HDL structure was assessed in patients with active RA (ACR criteria), PsA (CASPAR criteria) and SA (ASAS criteria) patients before initiating first biologic and in healthy controls matched for age, sex and body mass index. Dyslipidemia treatment or pathology which could interfere with lipid profile were excluded. Demographics data, disease activity, cardiometabolic profile and plasma samples were collected. HDL particle were isolated from plasma after two step ultracentrifugation using gradient of density. Lipidomics analysis were performed using liquid chromatography coupled with mass spectrometry. Phospholipid composition between patients and controls was compared using multivariate analyses to take into account possible confounding variables determined according to univariate results and clinical relevance (age, tobacco consumption, steroids use). Multidimensional analyses as factorial mixed data analysis (FMDA) were performed to complete these analyses.

Results: 19 RA, 19 PsA and 12 SA were analyzed (table 1). 220 phospholipids species were identified among which 2 major classes were modified in rheumatic diseases. Phosphatidylcholine (PC) decreased in RA and PsA ($p<0.01$ and <0.05 respectively) while lysophosphatidylcholine (LPC) increased significantly ($p<0.01$, and <0.05 respectively). Some phospholipids species as PC 40: 8 ($p<0.001$), LPC 16:0 ($p<0.001$), LPC 18:0 ($p<0.001$) were identified as discriminant marker of HDL composition in rheumatic disease as compared to controls.

	RA (mean±SD)	Controls (mean±sd)	PsA (mean± sd)	Controls (mean±sd)	SA (mean±sd)	Controls (mean±sd)
Number of patients	19	18	19	17	12	12
Age	55.32 ±10,91	58.78 ±4,61	49.63± 8.04 **	57.65±4.77 **	45.33±6.56 ***	57.17±5.69***
Sexe (W/M) (%M)	1/18 (5,3%)	1/17 (5,5%)	10/9 (53%)	10/7 (58%)	8/4 (67%)	8/4 (67%)
BMI (kg/m²)	24.22 ±4,81	22.13 ±2,92	27.78± 7.60	24.55±3.63	25.49±4.16	23.69±2.92
ApoB/ApoA1	0.67 ±0,15	0.63 ±0,15	0.77± 0.21	0.75±0.14	0.74±0.12	0.75±0.17
CRP (mg/L)	31.16 ±43,98 ***	0.80 ±0,72 ***	19.74±17.33 ***	1.40±1.83 ***	2.88±1.97 *	1.91±2.17 *
CV family history Y/N (%)	1/18 (5,3%)	0/18 (0%)	1/18 (5,2%)	0/17 (0%)	0/12 (0%)	0/12 (0%)
CV personal history Y/N (%)	0/19 (0%)	0/18 (0%)	0/19 (0%)	0/17 (0%)	0/12 (0%)	0/12 (0%)
High blood pressure Y/N (%)	4/15 (21%) *	0/18 (0%) *	2/17 (11%)	0/17 (0%)	4/8 (33%) *	0/12 (0%) *
Diabetes mellitus Y/N (%)	1/18 (5,3%)	0/18 (0%)	1/18 (5,2%)	0/17 (0%)	0/12 (0%)	0/12 (0%)
Current tabacco use Y/N (%)	5/14 (26%) *	0/18 (0%) *	5/14 (26%)	0/17 (0%)	6/6 (50%) **	0/12 (0%) **
Disease duration (years)	6,68±6,33					
DAS 28 CRP score	4.56 ±1,45		4.00± 0.99			
BASDAI			55.67±18.58		61.14±14.09	
Corticosteroid treatment Y/N (%)	10/9 (53%)		2/17 (11%)		1/11 (8,3%)	
NSAI treatment Y/N (%)	9/10 (47%)		6/13 (32%)		6/6 (50%)	
Methotrexate treatment Y/N (%)	15/4 (79%)		9/10 (47%)		1/11 (8,3%)	

Table 1 : Demographics data, cardiometabolic profile and diseases caracteristics

* p<0.05, **p<0.01, ***p<0.0001 using T test or Chi-squared

Conclusions: Phospholipids composition of HDL is altered in RA and PsA. These alterations could explain a loss of atheroprotective functions and the excess of CV risk observed in RA and PsA patients. Chronic inflammation, through the activation of phospholipase A2 type II which hydrolyze PC into LPC, could modify the structure of HDL phospholipids and thus could impact HDL functionality such as cholesterol efflux, LDL oxidation modulation, anti-inflammatory and vasculoprotective properties. These preliminary data suggest the major role of inflammation in these alterations.

References:

[1] Tselepis AD et al. Atheroscler Suppl. 2002;3(4):57–68.
[2] Kontush A, et al. J Lipid Res. 2013;54(11):2950–63.

Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2017-eular.5491

THU0040 NOVEL AKT ACTIVATOR SC-79 IS A POTENTIAL TREATMENT FOR ALCOHOL-INDUCED OSTEONECROSIS OF THE FEMORAL HEAD

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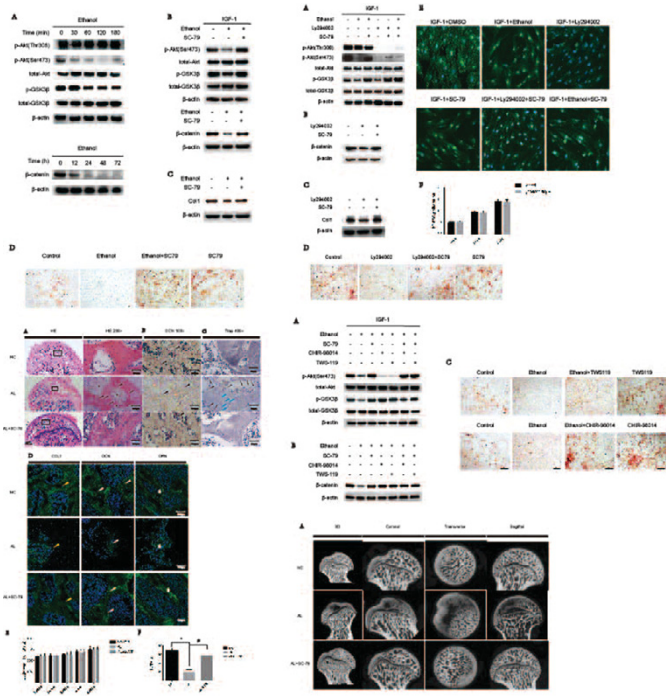
Background: Alcohol is known to be one ofthe leading risk factors for osteonecrosis of the femoral head. However, the underlying etiology and protective strategiesof alcohol-induced osteonecrosis of the femoral headhavenot been clarified.

Objectives: The aim of this study was to explore the molecular mechanism of alcohol-induced osteonecrosis of the femoral head, and to investigate the protective effect of SC-79 on the disease.

Methods: In vitro, we employed RT-PCR, alizarin red staining, alkaline phosphatase activity testing, western blot, immunofluorescence staining to investigate the effect of ethanol on hBMSCs. In vivo experiments, immunofluorescence staining, TRAP, TUNEL and micro-CT were performed to investigate the development of ONFH.

Results: In vitro, we found that ethanol could significantly impair the expression of osteogenic genes of RUNX2 and OCN, downregulate osteogenic differentiation, impair IGF-1 induced membrane recruitment of the Akt, suppress the Akt-Ser473 phosphorylationand the subsequent activation of Akt/GSK3β/β-catenin signaling in bone mesenchymal stem cells. Functional studies further confirmed this signaling was the critical mediator during the ethanol-induced inhibitory effects on osteogenesis of BMSCs.Thus, the dephosphorylation of Akt-Ser473 in Akt/GSK3β/β-catenin signaling pathway might be a potential mechanism in the pathogenesis of alcohol-induced osteonecrosis of the femoral head.SC-79, a novel Akt activator was introduced in this study to block the dephosphorylation effect of ethanol on Akt-Ser473 both in vitro and in vivo. In the rat model of alcohol-induced osteonecrosis of the femoral head, micro-CT and histopathological analyses revealed obvious osteonecrosis changes in alcohol-administrated rats while significantly less developed in SC-79 injected rats. OPN, OCN and COL1 immunofluorescence staining revealed that osteogenic response of femoral heads was markedly reduced after alcohol administration, but significantly reversed by SC-79 treatment.



Conclusions: Hence, we discovered alcohol-induced osteonecrosis of the femoral headwas associated with the suppression of the Akt-Ser473 in Akt/GSK3β/β-catenin pathway in BMSCs. The administration of SC-79, to elevate Akt activation, might be a clinical strategy to prevent the development of alcohol-inducedosteonecrosis of the femoral head.

Acknowledgements: The current study was supported by National Natural Science Foundation of China (81272003, 81301572) and SMC-Chen Xing Plan for Splendid Young Investigators of Shanghai Jiao Tong University.

Disclosure of Interest: None declared

DOI: 10.1136/annrheumdis-2017-eular.1927

THU0041 PROGRANULIN AND DERIVATIVES CAN BE EMPLOYED AS LATENT DUAL-FUNCTION CHONDROGENIC AND ANTI-INFLAMMATORY THERAPEUTICS FOR THE TREATMENT OF RHEUMATOID ARTHRITIS

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Background: Rheumatoid Arthritis (RA) is a debilitating inflammatory disease of the joints afflicting around 1% of Western populations. Some of the best treatments are anti-TNF agents, but these only achieve remission in 60% of patients and cause deleterious side effects. Progranulin (PGRN), a cysteine-rich, multi-domain growth factor was reported to bind TNF-receptors (TNFR) blocking pro-inflammatory signalling[2], as well as stimulating chondrogenesis[3]. PGRN is cleavable and its peptides have pleiotropic effects, some of which may be beneficial and others refractory to ameliorating RA. Granulin A (GRN A) was shown to interact with cartilage ECM protein COMP[4]. Atsttrin – comprising 3 fused PGRN regions, was shown to ameliorate arthritic disease[2]. The latency associated peptide (LAP) of TGFβ1 can be fused to short peptides and cytokines via a MMP cleavage site to facilitate targeting to inflamed sites such as RA joints, reducing side effects and enhancing *in vivo* half-life[1]. We hypothesised that a peptide based on PGRN could be fused to LAP and used to both block TNF and stimulate cartilage regeneration in RA joints in a targeted way.

Objectives: To produce a panel of PGRN derivatives fused to LAP. To determine the chondrogenic and anti-TNF capacities of the fragments in the presence and absence of MMP activation. To evaluate their efficacy in the CIA model of RA.