OP0246

MIR-214-3P PROTECTS AGAINST OSTEOARTHRITIS BY DIRECTLY TARGETING NF- κ B PATHWAY

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Background: Osteoarthritis (OA) is a degenerative disease associated with changes in the articular cartilage and bone, severely affecting patients' mobility and quality of life. Multiple factors including mechanical stress, metabolic alteration and inflammatory mediators are involved in the complex pathogenesis of OA[1]. Interventions targeting these pathogenic factors may contribute to the treatment of OA. MiRNAs are single strand non-coding small RNAs, which are regulated in chondrogenesis and OA[2,3]. Recent studies demonstrated that miRNAs are involved in the regulation of NF- κ B signaling pathway by different mechanisms[4]. These interactions suggest that NF- κ B related miRNAs may be used as potential biomarkers and drug therapeutic targets in clinical treatment of OA. However, the relationship between miR-214-3p and NF- κ B pathway remains poorly understood in OA.

Objectives: This study aimed to test the expression and biological function of miR-214-3p in OA, and explore its mechanism in osteoarthritic chondrocytes.

Methods: Articular primary chondrocytes were isolated from human cartilage samples, which were acquired from patients with end-stage knee OA at the time of total knee replacement surgery (n = 27), according to protocols approved by the Ethic Committee of Zhujiang Hospital. Real time PCR (RT-PCR) and in situ hybridization (ISH) were used to detect the expression of miR-214-3p in OA and non-OA cartilage tissues. Interference of miR-214-3p was conducted using inhibitor, while overexpression of miR-214-3p was performed with mimics. Metabolism of extracellular matrix was detected by RT-PCR, western blotting and immunofluorescence in vitro. Flow cytometry were conducted to determine cell apoptosis. A luciferase reporter assay, was used to evaluate the interaction between miR-214-3p and its downstream target. Human chondrocytes were cotransfected with miR-214-3p and the IKBKB-overexpressing plasmid to confirm the interaction between miR-214-3p and NF- κ B pathway. For in vivo studies, experimental OA was induced in 12-week-old male C57BL/6J mice by destabilization of the medial meniscus (DMM) surgery with miR-214-3p agomir intra-articular (IA) injection (once weekly for 12 days) or by IA injection (once weekly for 12 days) of miR-214-3p antiagomir. Mice were sacrificed 10 weeks after the first IA injection, and subjected to histological analyses.

Results: MiR-214-3p was significantly reduced in human OA cartilage. The decreased expression of miR-214-3p in the OA cartilage tissues was directly associated with excessive apoptosis and imbalance between anabolic and catabolic factors of ECM. Mechanistically, we determined that miR-214-3p directly targeted IKBKB/IKK- β and thereby suppressed the activation of NF- κ B pathway. IKBKB overexpression attenuated the inhibitory effect of miR-214-3p on NF- κ B pathway. Furthermore, inhibition of miR-214-3p in mice joints triggered spontaneous cartilage loss and OA development, while IA injection of miRNA-214-3p agomir alleviated OA in the DMM mouse model.

Conclusion: Our results reveal an important role of miR-214-3p in OA progression. MiR-214-3p was down-regulated while IKBKB was upregulated in OA. MiR-214-3p inhibits the NF- κ B signaling pathway and suppresses the progression of OA through targeting IKBKB. Thus, miR-214-3p maybe a therapeutic target for OA.

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Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2020-eular.5731

Progress in scleroderma and myositis

OP0247

PERSISTENT PREMATURE MORTALITY GAP IN IDIOPATHIC INFLAMMATORY MYOPATHY: A GENERAL POPULATION-BASED COHORT STUDY

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Background: Idiopathic inflammatory myopathy (IIM) is associated with significant premature mortality; however, whether the mortality gap has improved over recent years is unknown.

Objectives: To determine trends in premature mortality in patients with IIM in a large cohort, representative of the United Kingdom (UK) general population.

Methods: Using The Health Improvement Network (THIN), an electronic medical record database representative of the UK general population, we identified patients with incident IIM between 18 and 89 years of age (defined by at least one Read diagnosis code for dermatomyositis, polymyositis, or interstitial myositis with at least one year of continuous enrollment in THIN prior to the cohort entry date) and up to 10 controls without IIM matched on age, sex, birth year, and database entry year. The cohort was divided in two based on the year of IIM diagnosis: the early cohort (1999-2006) and the late cohort (2007-2014). We calculated adjusted hazard ratios for death using a multivariable Cox-proportional hazards model and adjusted rate differences using an additive hazard model.

Results: The early cohort consisted of 355 patients with IIM and 3182 matched controls, while the late cohort consisted of 396 IIM patients and 3551 matched controls. In both cohorts, IIM patients had excess mortality compared to matched controls [57.4 vs. 15.2 deaths/1000 person-years (PY) in the early cohort and 43.2 vs. 14.1 deaths/1000 PY in the late cohort] (Table). The corresponding multivariate mortality hazard ratios were 2.73 (95% CI, 1.85 to 4.03) vs. 2.61 (95% CI, 1.75 to 3.89) in the early and late cohorts, respectively (p-value for interaction = 0.63) (Figure). The absolute multivariate mortality differences were 36.6 (95% CI, 20.4 to 52.8) and 25.8 (95% CI, 13.7 to 37.9) deaths/1000 PY, in the early and late cohorts, respectively (p-value for interaction = 0.24).

Conclusion: In this general population-based cohort study, patients with IIM had over 2.5 times the risk of death compared to matched controls, even after adjusting for comorbidities and medications. Unlike trends seen in rheumatoid arthritis and granulomatosis with polyangiitis, there appears to be no improvement in mortality in IIM in recent years. This highlights the need for improved strategies for the management of patients with IIM and its comorbidities.

Table. Association between idiopathic inflammatory myopathy (IIM) and all-cause mortality according to time period.

	1999-2006		2007-2014		p-value for interaction
	IIM cohort (n=355)	Non-IIM cohort (n=3182)	IIM cohort (n=396)	Non-IIM cohort (n=3551)	
Follow-up time, years (mean $\pm$ SD)	2.6 $\pm$ 2.1	2.9 $\pm$ 2.1	3.2 $\pm$ 2.4	3.5 $\pm$ 2.4	
Number of deaths	53	140	55	177	
Death rate/1000 PY (95% CI)	57.4 (43.0, 75.1)	15.2 (12.7, 17.9)	43.2 (32.5, 56.2)	14.1 (12.1, 16.3)	
Age-, sex-, and entry year-matched hazard ratio (95% CI)	4.02 (2.89, 5.59)	1.00 (ref)	3.43 (2.49, 4.73)	1.00 (ref)	0.50
Multivariable-adjusted hazard ratio (95% CI)*	2.73 (1.85, 4.03)	1.00 (ref)	2.61 (1.75, 3.89)	1.00 (ref)	0.63
Age-, sex-, and entry year-matched rate difference/1000 PY (95% CI)	42.2 (26.6, 57.9)	0.0 (ref)	29.1 (17.5, 40.7)	0.0 (ref)	0.24
Multivariable-adjusted rate difference/1000 PY (95% CI)	36.6 (20.4, 52.8)	0.0 (ref)	25.8 (13.7, 37.9)	0.0 (ref)	0.24

* Multivariable models were adjusted for age, sex, entry year, number of GP visits, BMI, smoking status (i.e., non-smokers, ex-smokers, current smokers), alcohol consumption (i.e., non-drinkers, ex-drinkers, current drinkers), comorbidities, and medication use.

PY, person-year; BMI, body mass index; GP, general practitioner