STRESS-ACTIVATED MIR-204 GOVERNS SENESCENT PHENOTYPES OF CHONDROCYTES TO PROMOTE OSTEOARTHRITIS DEVELOPMENT

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Background: A progressive loss of cartilage matrix leads to the development of osteoarthritis (OA). Matrix homeostasis is disturbed in OA cartilage as the result of reduced production of cartilage-specific matrix and increased secretion of catabolic mediators by chondrocytes. Chondrocyte senescence is a crucial cellular event contributing to such imbalance in matrix metabolism during OA development.

Objectives: We sought to identify a previously unknown, senescence-associated signaling pathway in chondrocytes linked to major OA cartilage manifestations such as PG loss and cartilage degeneration.

Methods: We particularly aimed to screen miRNAs whose inhibition could effectively modulate senescent phenotypes of chondrocytes to treat OA. We investigated the regulatory mechanisms of miR-204 under various stress-eliciting stimuli in primary cultured human and mouse chondrocytes. We examined the in vivo effects of miR-204 overexpression and its antagonism in surgically induced OA mouse models. DMM surgery was used to induce posttraumatic OA in 12-week-old mice. Small RNAs were delivered to mouse knee joints by intra-articular injection. Various OA manifestations including cartilage destruction, subchondral bone sclerosis, osteophyte maturity, and synovial inflammation in mice were histologically inspected.

Results: We identify miR-204 as a senescence-associated microRNA (miRNA) which is markedly upregulated in OA cartilage. The upregulated miR-204 simultaneously targets multiple components of the sulfated proteoglycan (PG) biosynthesis pathway, effectively shutting down PG anabolism. Ectopic expression of the miR-204 in joints triggers spontaneous cartilage loss and OA development, whereas inhibition of miR-204 ameliorates experimental OA, with concomitant recovery of PG synthesis and suppression of inflammatory senescence-associated secretory phenotype (SASP) factors in cartilage.

Conclusion: We unravel a stress-activated senescence pathway that underlies disrupted matrix homeostasis in OA cartilage.

Disclosure of Interests: None declared.

References:

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Table 1. Remission levels considered in the study (1).

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Chronic damage was registered according to SLICC damage index (SDI). All the patients were evaluated at baseline (T0) and every 12 months (T1, T2, T3, T4). At each time-point, we calculated the prevalence of LupusCDC, defined as remission achievement and chronic damage prevention. Even though activity and damage are intimately connected, to date indices including both these outcomes are not available.

Objectives: In the present study, we aimed at assessing the application of a new index, the Lupus comprehensive disease control (LupusCDC), including disease activity and chronic damage progression.

Methods: We performed a longitudinal analysis, including SLE patients according to ACR 1997 criteria, followed-up in the period between January 2014 and December 2018, and with at least one visit per year. Disease activity was assessed by SLE Disease Activity Index 2000 (SLEDAI-2K) and three different remission levels were evaluated, as reported in Table 1 (1).


Figure 1. Proportion of patients achieving one of the three levels of remission (A), and of patients reaching LupusCDC according with different remission levels (B).

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Results: According with inclusion criteria, 172 SLE patients were evaluated in the present analysis [M/F 16/156, median age 49 years (IQR 16.7), median disease duration 180 months (IQR 156)]. At first assessment, we observed a mean±SD SDI value of 0.7±1.1. In details, 56 patients (32.5%) showed damage in at least one organ/system and the presence of damage was significantly associated with age (p=0.0001, r=0.3) and disease duration (p=0.0003, r=0.3). During the follow-up, we observed a significant increase in SDI values compared with T0 (T1: mean±SD 0.8±1.3, p<0.0001; T2: 0.8±1.4, p<0.0001; T3: 0.9±1.4, p=0.0001; T4: 1.0±1.5, p<0.0001).

In figure 1A and 1B we reported the proportion of patients achieving the different levels of remission and LupusCDC, respectively. In particular, the LupusCDC definition including CR was the most frequently detected in all time-points evaluated (T1: 18.0%; T2: 31.9%; T3: 27.9%; T4: 24.4%), with a significant difference at T2 [LupusCDC(CR) versus LupusCDC(CIR-GCoff), p=0.0002; LupusCDC C(CR) versus LupusCDC(CIR-GCon) p=0.0002], T3 [LupusCDC(CR) versus LupusCDC(CIR-GCoff), p=0.006], T4 [LupusCDC(CR) versus LupusCDC(CIR-GCon), p=0.002]. No significant differences were found when comparing the prevalence of different remission levels and the prevalence of LupusCDC including the corresponding remission.

Conclusion: In the present analysis we proposed for the first time a new index including disease activity and chronic damage, in order to evaluate the proportion of SLE patients reaching a comprehensive disease control. We found that CR is most frequently associated with the absence of damage progression.


Figure 1. Proportion of patients achieving one of the three levels of remission (A), and of patients reaching LupusCDC according with different remission levels (B).