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Inhibition of osteoclastogenesis and inflammatory bone resorption by targeting BET proteins and epigenetic regulation

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Epigenetics is becoming increasingly appreciated as a new area of research that may provide insights into the pathogenesis of inflammatory autoimmune diseases such as rheumatoid arthritis (RA). Epigenetics refers to the control of gene expression by chromatin regulators, modifications of chromatin components such as histones, DNA methylation, or non-coding RNAs. Recent drugs targeting epigenetic processes have shown great promise for the treatment of cancers and inflammatory conditions. Receptor activator of nuclear kappa B ligand (RANKL) is a key inducer of osteoclastogenesis and emerging evidence suggests that RANKL-induced histone modifications are important for osteoclastogenesis. However, these epigenetic mechanisms in osteoclasts are not well understood and have not been therapeutically targeted. Thus, we have investigated the epigenetic regulation of osteoclast differentiation. We find that the small molecule inhibitor, I-BET151 that targets bromo and extra-terminal (BET) proteins that 'read' chromatin states by binding to acetylated histones strongly suppresses osteoclastogenesis. Interestingly, I-BET151 attenuates inflammatory arthritis by diminishing both inflammation and bone resorption and protects mice from oestrogen deficiency induced osteoporosis. Through transcriptome analysis, we reveal an important role of a MYC/NFAT axis in osteoclasts that is elevated in RA osteoclast precursors. I-BET151 suppresses osteoclastogenesis by, in part, inhibiting a MYC/NFATc1 axis. These findings implicate the importance of MYC and BET proteins in osteoclast differentiation and demonstrate that targeting an epigenetic molecule in osteoclasts can be effective in suppressing the pathological bone resorption. Taken together, our study opens up a new line of investigation in the understanding and therapeutic targeting of pathological bone resorption..

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Risk of multiple sclerosis during tumour necrosis factor inhibitor treatment for arthritis- A population based study from DANBIO and the Danish Multiple Sclerosis Registry

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Background: Evidence of tumor necrosis factor-α (TNF) as an important factor in the pathogenesis of multiple sclerosis (MS) has emerged. However, attempts of treating MS with TNF-inhibitors (TNFi) have increased disease activity.

Objectives: To investigate whether TNFi treatment in arthritis patients is associated with an increased risk of developing MS and if rheumatoid arthritis (RA) is associated with a decreased risk compared to the general population.

Methods: Data from the national DANBIO Registry and the Danish Multiple Sclerosis Registry was linked. A cohort of 27,875 patients with arthritis (64% RA patients) was followed up for MS. During follow-up 2000-2012, 10,296 patients started TNFi therapy. Standardized Incidence Ratios (SIR) of MS was estimated using standardized incidence rates from the general populations and person-years at risk.

Results: During 113,527 person-years, 12 incident MS cases occurred in the cohort, overall SIR=1.11(95% CI 0.63-1.96). SIR for arthritis patients ever treated with TNFi therapy was 1.38(95% CI 0.69-2.77, N=8) and 0.80(95% CI 0.30-2.12, N=4) in never treated. An increased risk was observed in males treated with TNFi (SIR 3.48 95% CI 1.45-8.37) and in ankylosing spondylitis (AS) patients (SIR3.91 95%CI 1.47-10.42).The SIR for all RA patients was 0.65(95%CI 0.24-1.72).

Conclusions: We found no overall association between RA and MS. No overall increased rate of MS was seen in TNFi exposed arthritis patients, but TNFi treated AS and male patients had an increased MS risk. However, low statistical power and diagnostic delay of MS should be taken into consideration when interpreting these results.

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