

## Role of nerve growth factor and tropomyosin receptor kinase A in the pathogenesis of osteoarthritis. Might nerve growth factor be the link intertwining obesity and osteoarthritis?

We read with interest the paper by Nwosu *et al*<sup>1</sup> recently published in *Annals of the Rheumatic Diseases*. They clearly provided evidence that blocking tropomyosin receptor kinase A (TrkA), the p140 high-affinity receptor of nerve growth factor (NGF), by a selective TrkA inhibitor AR786 relieves pain in two different rat models of osteoarthritis (OA). A reduction of synovitis was also shown by histopathology, suggesting that NGF inhibition exerted its effect at peripheral level on extraneural tissues. Authors concluded that inhibition of NGF activity might be an effective strategy as treatment of OA pain. Indeed, NGF may have pleiotropic effects, and we would like to speculate on the possible role played by NGF and its counter-receptor TrkA also in cartilage metabolism. Some years ago, we showed that human chondrocytes synthesise NGF and TrkA, and that their expression is regulated in OA cartilage.<sup>2</sup> We studied the articular cartilage from three healthy donors (HDs) and 12 patients with OA undergoing surgical knee replacement. According to the extent of macroscopic and microscopic (Mankin score) damage, OA cartilage was split in two zones showing the lowest (low) and highest (high) degree of anatomic injury. Flow cytometry analysis on freshly isolated chondrocytes showed an increasing expression of intracellular TrkA from HD cartilage ( $3.4 \pm 1\%$ ) to low ( $31 \pm 11\%$ ) and high OA cartilage ( $41.4 \pm 19\%$ ), respectively ( $p < 0.01$ ). Likewise, chondrocyte NGF expression was significantly higher in high ( $41.3 \pm 25\%$ ) or min ( $21.3 \pm 12\%$ ) OA cartilage than in HDs ( $3.8 \pm 2.4\%$ ,  $p < 0.01$ ). The autocrine production of NGF by chondrocytes was further confirmed by real time-polymerase chain reaction (RT-PCR), detecting higher NGF mRNA expression in OA cartilage. NGF and its receptor TrkA are also produced by human adipocytes from white adipose tissue.<sup>3</sup> These findings have been further confirmed, and an increase in NGF plasma levels in obese women correlating with body mass index (BMI) and inflammatory markers was also reported.<sup>4</sup> We are focusing on possible inter-relations between cartilage damage, BMI and NGF in human OA.<sup>5</sup> We analysed knee articular cartilage from 19 obese patients with OA (13 female, BMI  $31\text{--}37 \text{ kg/m}^2$ , age 41–84 years) and 10 normal-weight patients with OA (six female, BMI  $21\text{--}23 \text{ kg/m}^2$ , age 28–73 years). Cartilage injury was assessed by Osteoarthritis Research Society International (OARSI) score<sup>6</sup> and NGF expression by semiquantitative immunohistochemistry and real-time quantitative reverse-transcriptase polymerase chain reaction (RTQ-PCR) analysis. We found a significant correlation between OARSI score and BMI ( $r=0.64$ , 95% CI 0.35 to 0.82). Immunohistochemistry showed a correlation between NGF expression and BMI ( $r=0.76$ , 95% CI 0.53 to 0.88) or OARSI score ( $r=0.82$ , 95% CI 0.65 to 0.91). These findings were confirmed by RTQ-PCR analysis.

The role of NGF in chondrocyte metabolism is unknown, but being adult cartilage aneural, it is conceivable that it is not

linked to perception of pain or other nervous system-related functions. Like in other cells,<sup>3, 7</sup> NGF might interact with growth factors and cytokines such as tumour necrosis factor (TNF)alpha and transforming growth factor (TGF)β-1, whose role in the pathophysiology of cartilage has been extensively studied.<sup>8</sup> Although Nwosu *et al* did not detect any impact on cartilage in OA rats by TrkA inhibition, we believe the TrkA/NGF targeting may represent a promising strategy in the treatment of OA, including pain.

Florenzo Iannone,<sup>1</sup> Simone Perniola,<sup>1</sup> Giuseppe Lopalco,<sup>1</sup> Luca Cantarini,<sup>2</sup> Giovanni Lapadula<sup>1</sup>

<sup>1</sup>Rheumatology Unit, University of Bari, Bari, Italy

<sup>2</sup>Rheumatology Unit, University of Siena, Siena, Italy

**Correspondence to** Professor Florenzo Iannone, School of Medicine, University of Bari, P.zza G. Cesare 11, Bari 70124, Italy; florenzo.iannone@uniba.it

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