The Early Inflammatory Response Directs the Healing of Osteochondral Injuries in the Synovial Joint

Johanna Bolander1,2,3,4, AnnaLisa Wilson1, Emma Parsons1, Cara Clouse1, Gustavo Moviglia1,3, Gary Poehling1, Liesbeth Ory4, Tim Herpelinck4, Frank Marini1 and Anthony Atala1.

1Berlin Institute of Health Centre for Regenerative Therapies (BCRT), Berlin Institute of Health at Charité - Universitätsmedizin Berlin, Berlin, Germany. 2IMEC, Kapeldreef 75, 3001 Leuven, Belgium. 3Wake Forest Institute for Regenerative Medicine, Winston-Salem, NC, USA. 4Skeletal Biology and Engineering Research Center, KU Leuven, Leuven, Belgium. 5Civil Association of Research and Development of Advanced Therapies (ACIDTA), CABA, Argentina.

Disclosures: Authors have no disclosure to report

INTRODUCTION: Osteoarthritis (OA) is a common degenerative disease, affecting over 520 million people worldwide (1, 2, 3). Due to its degenerative nature, OA causes severe pain, functional loss, and disability, with the synovial knee joint as the most affected site. Despite its high prevalence, substantial socio-economic impact and tremendous ongoing research efforts, we are still lacking effective therapies that can stop or prevent disease progression. A reason for this is our limited understanding regarding the initial cause and subsequent OA pathophysiological mechanisms. OA is commonly initiated by wear and tear or trauma that fails to heal, leading to a prolonged inflammatory response in the local environment. It has been shown that this inflammation leads to i) articular cartilage degeneration, ii) subchondral bone sclerosis, iii) synovitis, and iv) innervation by pain sensing neurons (4). Identifying the initial cause and subsequent signalling events that leads to OA initiation would enable improved diagnostic and therapeutic targets (5).

METHODS: To investigate the underlying mechanism of failed joint injury, small (SD) and large (LD) full-thickness osteochondral defects (OCD) were created in the trochlear groove of 10-week old female rats. Healing was characterized after 96-hours, one, four and twelve weeks post defect creation. Pathological evaluation upon OCD creation confirmed four distinct degrees of healing after 12 weeks depending on defect size and immune status. Animals receiving the SD injury displayed functional healing, while LD animals resulted in severe OA. Furthermore, the healing outcome of both the SD and LD injuries was further impaired in animals lacking mature T-cells.

RESULTS: Analysis of the early mechanism of healing one week post OCD creation confirmed a corresponding trend between the healing potential to extracellular matrix (ECM) production, progenitor- and immune cell activation. These results confirmed that both the availability of mature T-cells and defect size significantly affects the healing potential at an early phase of healing (p<0.5). Interestingly, scRNASeq confirmed unique inflammatory and progenitor cell populations present within the defect area in the functional SD healing model. To test whether the pro-inflammatory environment in the non-healing models was the underlying cause for the failed tissue regeneration, an immunomodulatory cell treatment was developed based on joint-activated and pro-regenerative immune cells that was co-cultured with placenta derived progenitor cells. The treatment was injected intra-articularly one week post OCD creation and evaluation in regards of treatment efficacy for OA resolution was evaluated after 11 weeks. It was confirmed that the immunomodulatory cell treatment improved the OCD healing potential in the three models of dysfunctional healing, with a fully regenerated articular unit confirmed based on histology, OARSI scoring and IHC analysis for Collagen type 2 and Lubricin.

DISCUSSION: These results confirm the integral role of the balanced activation of lymphocytes and progenitor cells for functional osteochondral regeneration and restored joint homeostasis. Furthermore, the presented findings show effective, stable articular cartilage regeneration after the intra-articular injection of an immunomodulatory cell treatment upon acute moderate to large osteochondral defects.

SIGNIFICANCE/CLINICAL RELEVANCE: The presented research provides a model where functional and dysfunctional osteochondral tissue repair can be studied in parallel. This allows to decipher molecular, cellular ECM-based alterations that lead to the two healing pathways and thus the opportunity identify diagnostic and therapeutic targets for early clinical intervention. In addition, the immunomodulatory therapy provide an early intervention therapy to avoid the initiation of post-traumatic OA.