ENHANCED BONE HEALING AND IMMUNOMODULATION

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TO THE EDITOR:

There are numerous experimental studies on the effects of immune modulation on the skeleton but few clinical ones.

In this letter, we supplement previous information on enhanced bone healing. A new branch of medicine, osteoimmunology, describes fracture healing as an active immune system process evolving in a cascade of repairs.

STAGES OF THE CASCADE

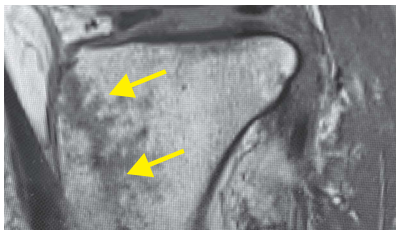
The first stage of bone repair is the *inflammation stage*, which includes macrophages and protective cytokine secreting T-cells. This stage is followed by the *reparation stage*, which includes soft cartilage to hard bone. The last stage is the *regeneration stage*, which includes osteosynthesis [Figure 1].

In the normal repair of disturbed organic tissue, only the bone does not leave a scar. However, bone could be interfered with, diminished, or perhaps as in our case, enhanced. In 2004, the identification of deficiency in lymphocyte T-cells was found to induce profound osteoclastogenesis, with resulting osteopenia [1].

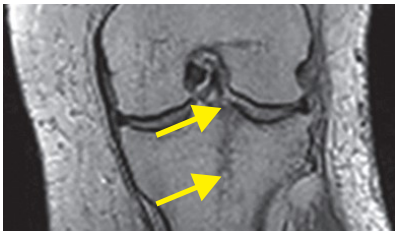
The field of osteoimmunology introduced a shift from the pure endocrine approach of bone regeneration to a metabolic one [2]. Inflammation was thought to lead to immune-skeletal variation, disturbing the bone regenerating balance and causing osteoporosis or autoimmune diseases. This inflammation is also present in malignancies [3]. Apart from inflammatory reaction, the protective, cytokine secreting T-cells were also found to heal the bone. This programmed death cell LA (PD-1) protein, a checkpoint inhibitor, was elevated, mainly in the second stage of bone repair. PD-1 disturbed the osteoclastic activity, leading to bone po-

Figure 1. A fractured tibial condyle, traumatic in origin, a vertical metaphyseal split and a transverse fracture reaching horizontally until the lateral cortex (diagnosed as Gr. I-II in Schatzker fracture classification). The patient was receiving immunotherapy for melanoma. Subsequent radiological studies, X-ray, computed tomography scans, and magnetic resonance imaging scans documented a full healing process within 32 days

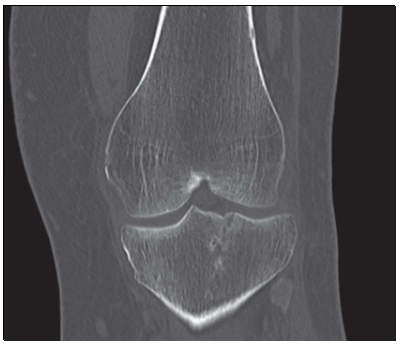
[A] Enhanced bone healing was observed, despite no immobilisation and full weight bearing in a patient with lymphoedema on her leg from previous groin dissection



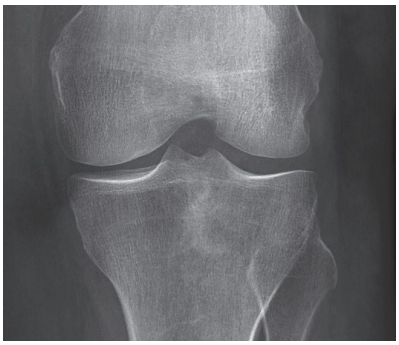
[B] Complex vertical fracture of the proximal tibial metaphysis extending to the articular surface of the lateral tibial plateau (lateral and PA views)



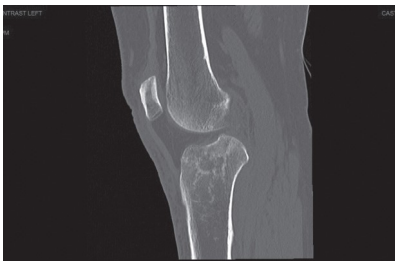
[C] Bone structure during the repairing stage almost refilling the fracture space



[D] Fracture line almost closed



[E] Computed tomography scan 32 days post trauma with an obliterated fracture line. Near complete healing of the previously demonstrated lateral tibial plateau fracture with mature bony remodelling at the site of a prior condylar fracture and complete resolution of bone marrow oedema



rosis and indirectly increasing the osteoblastic activity. The result was increased bone regeneration within both trabecular and cortical mineral density, which was defined as osteopetrosis [1].

Elevated PD-1 levels were also found in a group of post-menopausal women who had been diagnosed with osteoporosis [4].

The concept of increased bone genesis, while PD-1 production was depressed, was observed in patients treated with pembrolizumab (MK-3475, a humanized Ig G4 monoclonal antibody). Pembrolizumab is used in immunotherapy. It was observed in bone regeneration of non-malignant, traumatic bone insult. Our previously described clinical case shows additional radiological imaging [Figure 1E] [5].

The last stage is illustrated in a computed tomography scan 32 days post-trauma, with obliterated bony fracture line, suggesting full osteogenic repair that had edematous bone construct already 3 weeks after a tibial condyle fracture.

CONCLUSIONS

The three stages of bone repair according to osteoimmunology are inflammation, reparation, and regeneration. Immunotherapy might have increased bone regeneration within strong trabecular and cortical mineral density, which is interpreted as osteopetrosis.

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Capsule

New roles for an immune stalwart

Group 2 innate lymphoid cells (ILC2s) tend to reside in tissues where pathogens enter the body, and they contribute to immunity against parasite infection. Like other types of immune cells, excessive proinflammatory activity of ILC2s can contribute to disease. **Cui** et al. found that CD45, a transmembrane tyrosine phosphatase that is important for the development and activation of T cells, plays a role in restraining ILC2s. Deletion of CD45 in ILC2s increased cell numbers and maturation under steady-state conditions and triggered their hyperactivation during immune responses. This was associated with exacerbated lung inflammation and pathology in mouse models of asthma and pulmonary fibrosis. The results not only show the regulatory mechanisms underpinning ILC2s, but also reveal a previously unknown role for CD45 in the immune system.

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Eitan Israeli

Capsule

Aspirin for secondary prevention of cardiovascular disease

Yoo et al. evaluated aspirin use for secondary prevention of cardiovascular disease (CVD) across 51 low-, middle-, and high-income countries. The sample of participants included nonpregnant adults aged 40 to 69 years. The overall pooled sample included 124,505 individuals. The median age was 52 (IQR 45–59) years, 50.5% were women. A total of 10,589 individuals had a self-reported history of CVD. Among individuals with a history of CVD, aspirin use for secondary prevention in the overall pooled sample was 40.3%. By income group, estimates were 16.6% in low-income countries, 24.5% in lower-middle-income countries, 51.1% in upper-middle-income countries, and 65.0% in high-income countries. Worldwide, aspirin is underused in secondary prevention, particularly in low-income countries. National health policies and health systems must develop, implement, and evaluate strategies to promote aspirin therapy.

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