Controlled Early Inflammation and Bone Healing—Potential New Treatments

In dental school, we were taught the scientific principle "inflammation is necessary for healing". This principle needs to be updated due to the further characterization of the role inflammation plays in the healing process.

Early bone healing occurs via specific cellular signaling events: (i) proinflammatory, (ii) anti-inflammatory, (iii) proangiogenic, and (iv) osteogenic.[1] Research has increased our understanding of the connection between the immune system and bone healing.[2–6] The significance of controlling the *immediate* inflammatory response for successful bone formation has been confirmed.[7] When an osteotomy is performed, multiple proinflammatory cytokines (1st signaling event) are stimulated, such as interleukin (IL)-1α, IL-1β, IL-6, and tumor necrosis factor alpha (TNF-α). Einhorn et al.[8,9] identified this early inflammatory cytokine expression profile in 2002 and 2003; however, the down-regulation or modulation of cytokine expression was not considered until more recently. Controlling cytokine expression (inflammation) can help create the *ideal* environment for healing and bone formation. If the cytokine expression is not in a proper balance, compromised bone healing is observed.[1]; for example, excessive concentrations and time-exposure of TNF-α can lead to delayed bone formation.[10] Franchimont et al.[11] controlled the level of TNF-α by increasing the release of the anti-inflammatory cytokine IL-10 (2nd signaling event), thus creating a positive environmental impact at the surgical site. IL-6 has been shown to have a bi-phasic pro- or anti-inflammatory concentration-dependent effect on bone healing.[12,13]

Other events necessary for healing include the migration to, and accumulation of, stem and osteoprogenitor cells at the surgical site. The accumulation and activation of these osteogenic cells (4th signaling event) are dependent upon angiogenesis (3rd signaling event). Proinflammatory cytokines in the surgical site can inhibit stem cell differentiation and therefore bone formation.[7] Controlling inflammation is thought to have a positive effect on all signaling events.

Modulating the immune response during early bone formation may provide a favorable environment for improved predictability of bone grafting procedures. Schmidt-Bleek et al.[1] concluded: "The modulation of the immune response is a promising approach to improve bone regeneration." This greater understanding of the interconnection between the immune system and bone healing may well play a significant role in the future of implant dentistry. As clinicians, our responsibility is to provide efficient and predictable treatments with minimal discomfort; modulating the inflammatory response may be instrumental in meeting these treatment goals.

Strategies to control the immune response will undoubtedly be forthcoming and play an important role in our clinical practices.

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