

## INFLAMMATION

## Fetal bone growth directly and locally impaired by IL-6

IL-6 suppresses bone growth directly at the growth plate, and IL-1 $\beta$  and TNF work synergistically to trigger this effect by stimulating local IL-6 production. “Our experimental data strengthen the clinical observation of an association between high maternal IL-6 levels and impaired fetal growth,” reports lead investigator Lars Sävendahl from the Karolinska Institutet.

High maternal levels of IL-6, as seen in the serum of patients with rheumatoid arthritis, have previously been associated with low birth weight deliveries. “Attempts have been made to understand how inflammatory cytokines impair bone growth, but any local effects on the growth plate were not clarified” explains Sävendahl.

Here, the researchers performed microsurgery on fetal rat metatarsal bones, cultured them with and without cytokines, and monitored bone growth over 12 days. “This unique study allowed us to investigate the local, direct effects of cytokines on bone health,” says Sävendahl.

“The organ culture system of fetal metatarsal bones is an ideal *ex vivo* model system to follow bone growth in a real-time manner under the microscope.”

Exposure to IL-6 and its soluble receptor, IL-6Ra, decreased growth of the bone samples by 21% ( $P < 0.001$ ). Notably, a 27-fold increase in IL-6 production was detected in the supernatants of bones cultured with both IL-1 $\beta$  and TNF, in comparison with samples to which no cytokines were added. Individually, the mediators had minimal effects on bone growth; thus, the findings support the previously reported synergistic effect of these cytokines on IL-6 production.

The next step, report the researchers, will be to attempt to block this suppressive effect on bone growth by developing molecules that can directly target IL-6 production or signalling. The investigators were unable to rescue bone growth in this model with IL-6 antibody treatment—possibly because the antibody is unable to penetrate the growth

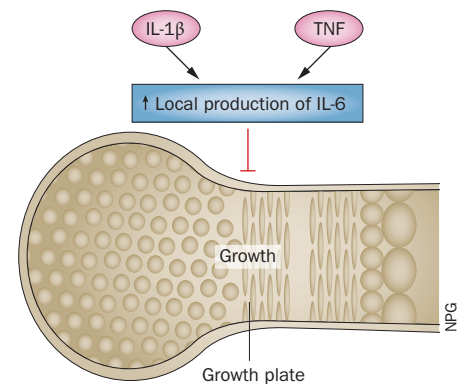


plate. Thus, suggests Sävendahl, it will be important “to develop small molecules or peptides directed towards the blocking of IL-6 to rescue bone growth.”

Bryony Jones

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