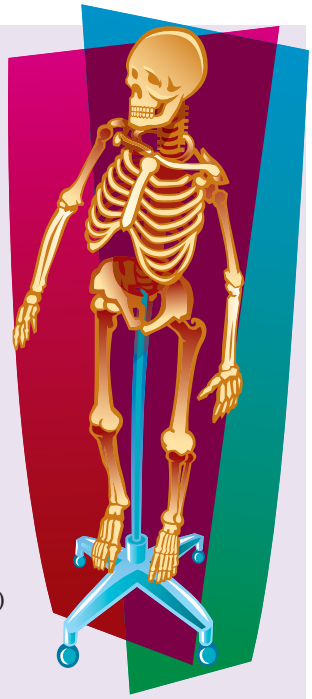
Proteins: Bone-bound



Several protein growth factors have been identified as bone-stimulating agents and potential therapies for conditions such as osteoporosis. However, extraskeletal organs like the liver and kidney rapidly take up proteins in circulation, inhibiting delivery to the bones and causing unwanted side effects. To get around this problem, the affinity of recombinant proteins to mineralized tissue must be enhanced.

Working to that end, Hasan Uludag and colleagues at the University of Alberta (Edmonton) are using the bisphosphonate (BP) compound 1-amino-1,1-diphosphonate (aminoBP) as a protein drug carrier. BPs have exhibited exceptional bone affinity. In a recent study, Uludag and colleague Jennifer Yang systemically administered aminoBP conjugates of recombinant bovine serum albumin (BSA) and lysozyme (LYZ) and showed their clear preferential behavior for targeting bones (*Biotechnol. Prog.* **2002,** *18,* 604–611).

The researchers injected protein–aminoBP conjugates and unconjugated proteins intravenously, and measured deposits in bones and other organs over several time increments. For BSA injections, the conjugate resulted in a 2- to 3.7-fold increase in delivery to the tibia and femur bones compared with the nonconjugate over one day, while bone delivery was enhanced 3.7- to 5.6-fold by aminoBP–LYZ over three days. BSA and aminoBP–BSA were also injected into rats with a model version of osteoporosis, and the conjugate improved bone delivery 2.2- to 7.5-fold.

Measurements were also taken at the kidneys, liver, and spleen. Generally, lower levels of the conjugates than the nonconjugates were detected at these organs, but results did not necessarily correlate with the bone deposit data. For example, 3 h after the BSA injections in normal rats, the bone measurements were already clearly in favor of the conjugate, but the liver and spleen still showed similar levels of the conjugate and nonconjugate. But by 24 h, there was a lower uptake of aminoBP–BSA at the liver and spleen, as well as the kidney. The authors surmised that the pharmacokinetics of the individual proteins play an important role in extraskeletal organ delivery.

BSA and LYZ are not bone growth stimulators, but only model compounds used to mimic the range of activity of potential therapeutics. To determine the effect of BP conjugation on biological activity, actual bone regenerators such as transforming growth factors and bone morphogenetic proteins must be explored in this context.

—DAVID FILMORE

Waste makes paste?

Many scientists consider so-called junk DNA to be an evolutionary scrap heap—the remnants of abortive gene duplications, silenced genes, run-amok repeat sequences, and transposons (so-called jumping genes). According to John V. Moran, an assistant professor at the University of Michigan Medical School (Ann Arbor), fully 17% of human DNA is made up of transposable long interspersed (LINE-1 or L1) elements that have, until now, been relegated to this junk category.

L1 elements replicate themselves in the human genome by using a form of target-primed reverse transcriptase, somewhat similar to the way that retroviruses reproduce—through RNA-dependent complementary DNA production. Under normal circumstances, L1 requires an endonuclease (which is coded for by the element itself) to cleave a separate DNA site in the genome in order to provide an origin for a replication–insertion event. The cleavage site acts as a primer for reverse transcription of full-length L1 RNA by an L1-coded reverse transcriptase. The DNA inserts at the site of its transcription. In addition to these genes required for "jumping", L1 elements are characterized by frequent 5′ truncations, a 3′ poly(A) tail, and variable-length target site duplications (TSDs).

This willy-nilly replication seemed to place L1 elements on the side of parasitism rather than pertinence to the host cell. But in a recent paper (*Nat. Genet.* **2002,** *31* (2), 159–165), Moran and his collaborators at Louisiana State University (Baton Rouge) reported on a potentially useful function of L1 elements—as DNA repair agents in human cells. The authors showed how, in the absence of endonuclease-primed sites, L1 can act to reattach two strands of broken DNA to each other. This endonuclease-independent insertion results in atypical L1 structures, truncated at their 3′ ends and missing TSDs.

Because DNA breaks can be severely debilitating or lethal to individual cells, this repair function of L1 may account for a selective advantage, leading to the accumulation of these retrotransposons over evolutionary time. The ability of human L1 to accomplish such repairs has previously been demonstrated in yeast and in normal and DNA-repair-deficient mutant Chinese hamster ovary cell lines, but the *Nature* report is the first documentation of this phenomenon in human cells.

—MARK S. LESNEY

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