

building blocks of random handedness will contain mixtures of right- and left-handed blocks so complex that no two polymers will have identical stereochemistry. All the polymers will be chiral, but if one exists, it is unlikely that its mirror image will too⁵. For small polymers consisting of only a few building blocks, the number of possible combinations of right- and left-handed blocks is small, and the mirror images are easily formed. However, for a polymer comprising 20 building blocks there are almost a million possibilities, and an enormous number of blocks would be required to build all the possible mirror images. Biological molecules often have over 100 building blocks, pushing the limits of available materials and making it extremely unlikely that a molecule and its mirror image can be prepared in the same batch. If the sample of polymers contained some that were self-replicating, it is reasonable that the most efficient one will emerge, and only this homochiral polymer will exist⁶.

In complex organisms and living systems,

homochirality manifests itself in families of related biological molecules, such as the naturally occurring L-amino acids in a protein. The presumption here is that there is cooperativity among these biomolecules in their biopolymers or underlying structure. The polymer example above alludes to an optimum self-replicating polymer. Can we form a general rule that homochirality leads to optimal function? With regard to self-replication, this question can be addressed by stereochemical analysis and reaction engineering. However, engineering the parameters of biochemical processes to obtain appropriate stereoselectivity — choosing of the preferred mirror image — has not been trivial. Poor reaction selectivity and inhibition of replication have plagued researchers who would like to mimic life through protobiology⁷.

Ghadiri *et al.*¹ find a stereoselective reaction, between two chiral peptides, that uses the product of their coupling to replicate — a process known as ‘autocatalysis’. Their results indicate that this self-replicating

Daedalus

David Jones

David Jones, author of the Daedalus column, is indisposed.

system could perpetuate homochirality, because a left-handed template is competent to bring together only those fragments that are also left-handed. The authors also show that, even if only one out of 15 building blocks has opposite handedness, autocatalysis is significantly diminished. Such a result establishes that homochiral peptides are most efficient at autocatalysis.

The authors also found that even though a single ‘mutation’ with regard to handedness could hamper autocatalysis, the same mutant template was reasonably effective at catalysing the combination of two pure left-handed fragments. The combination of these results supports the idea that a polymer evolution experiment would ultimately result in homochirality of biological molecules. Furthermore, these results support a general principle that similarity in building blocks leads to higher-order structure, like the spiral shape of a ram’s horn or a crystal-lattice structure^{8,9}.

Given the fundamental nature and pervasive occurrence of chirality in biological and non-biological macromolecules, it is reasonable to postulate that homochirality existed long before the genetic information of life was encoded. Once in place, this sense of chirality perpetuated throughout early life systems and has become a part of complex biochemical processes such as translation and transcription. So the linear sequence of information on the genome is passed along owing to the three-dimensional structure of the DNA double helix, and must now include the coding for homochirality that we see in amino acids. We now have a model system that may bring us closer to understanding why we see cooperativity among homochiral biological molecules today.

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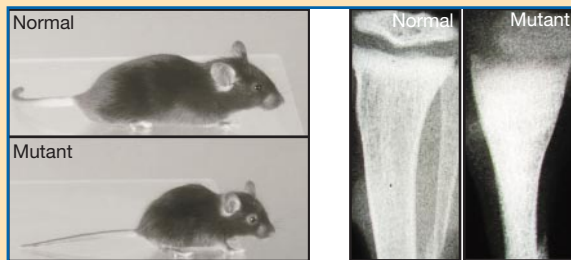
Medicine

Channel fault in osteopetrosis

Bone is a dynamic structure, constantly being formed (by cells called osteoblasts) and resorbed (by osteoclasts). The activities of these cells must be finely balanced. If resorption exceeds formation, the result is the weakened, brittle bones characteristic of osteoporosis.

In osteopetrosis, by contrast, not enough bone is resorbed: the osteoclasts malfunction, leading to dense yet fragile bones with no bone marrow. Writing in *Cell* (**104**, 205–215; 2001), Uwe Kornak, Dagmar Kasper and colleagues identify a molecule that is needed for the bone-resorbing cells to function. Their results may explain some cases of an inherited disease, infantile malignant osteopetrosis.

During bone resorption, osteoclasts attach to the bone matrix and form a specialized outer membrane, called the ruffled border, facing the bone. Bone-digesting enzymes are then transported out of the cell, across this border. The enzymes need an acidic environment to function, so the osteoclasts also pump out protons. At the same time, chloride ions are let out of



the cell to maintain the electrical balance. The protein-based channel that selectively allows the efflux of chloride ions has been elusive, but the authors suggest that it is a molecule called CIC-7.

Kornak *et al.* engineered mice with a disruption in the gene encoding CIC-7. The resulting mutant mice (one of which is pictured above, with a normal mouse) had all the characteristics of osteopetrosis, including short limbs and abnormally dense bones. The mice also failed to form bone marrow, as can be seen by comparing the two high-magnification X-ray images above. Moreover, osteoclasts isolated from the mutant mice were unable to absorb bone.

The authors tracked down the CIC-7 protein to the outer membrane and certain acidic organelles, called lysosomes, in the osteoclasts of normal mice. But there was no CIC-7 protein in these cells in the mutant mice. Although the osteoclasts from the mutant mice contained the usual proton pump in their outer membranes, they were unable to acidify the extracellular space — presumably because of the defect in CIC-7. Finally, Kornak *et al.* discovered that a patient with infantile malignant osteopetrosis has a disrupted CIC-7 gene. All in all, they make a convincing case that this chloride channel is crucial for bone resorption.

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