Biological Membrane Asymmetry and its Role in Bone Mineralization

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Abstract.
The membranes of animal cells consist of a bilayer of lipid molecules (phospholipids and cholesterol) and embedded protein molecules. However, in living cells the phospholipids are not distributed equally between the bilayer's cytoplasmic and extracellular leaflets. Phosphatidylserine (PS) and phosphatidylethanolamine (PE) are concentrated in the membrane's inner leaflet, whereas phosphatidylcholine (PC) and sphingomyelin (SM) are concentrated in the outer leaflet. This non-equilibrium situation is maintained by lipid pumps in the membrane, i.e., protein molecules which actively use energy in the form of ATP to transport lipids in both directions across the membrane. Pumps which transfer lipids from the external leaflet to the inner leaflet are termed *flippases.* Those that transfer lipids from the inner to the outer leaflet are termed *floppases*.

The asymmetric distribution of PS is particularly important because of the negative charge of its polar head. This allows it to interact with positively charged amino acid residues of peripheral and integral membrane proteins and with divalent metal ions in the neighbouring solution. Although normally maintained on the cytoplasmic side of the membrane by a PS-flippase, activation of *scramblase* proteins allows its distribution across the membrane to equilibrate, leading to PS exposure on the extracellular surface. In osteoblasts, the cells which produce bone, PS exposure also plays a key role in skeletal development. The negative charges of PS on the extracellular surface of their cells provides a template, attracting Ca^{2+} ions from the extracellular matrix and promoting the deposition of hydroxyapatite $Ca_{10}(PO_4)_6(OH)_2$, the major mineral component of bone.