Resumen

The mechanisms of Pb(II) toxicity have been studied in human red blood cells using confocal microscopy, immunolabeling, fuorescence-activated cell sorting and atomic force microscopy. The process follows a sequence of events, starting with calcium entry, followed by potassium release, morphological change, generation of ceramide, lipid fip-fop and fnally cell lysis. Clotrimazole blocks potassium channels and the whole process is inhibited. Immunolabeling reveals the generation of ceramide-enriched domains linked to a cell morphological change, while the use of a neutral sphingomyelinase inhibitor greatly delays the process after the morphological change, and lipid fip-fop is signifcantly reduced. These facts point to three major checkpoints in the process: frst the upstream exchange of calcium and potassium, then ceramide domain formation, and fnally the downstream scramblase activation necessary for cell lysis. In addition, partial non-cytotoxic cholesterol depletion of red blood cells accelerates the process as the morphological change occurs faster. Cholesterol could have a role in modulating the properties of the ceramide-enriched domains. This work is relevant in the context of cell death, heavy metal toxicity and sphingolipid signaling.