

P023 Inhibition of post-translational prenylation causes sustained activation of Rac, Cdc42 and Rho GTPases
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Nitrogen-containing bisphosphonate drugs (N-BPs) are the treatment of choice for common diseases characterised by bone loss, such as post-menopausal osteoporosis. These drugs act by inhibiting farnesyl diphosphate synthase, thereby indirectly preventing the prenylation of small GTPases required for the function and survival of bone-resorbing osteoclasts. Rather than inhibiting GTPase function, we have found that potent N-BPs cause an increase in the GTP-bound form of Rac, Cdc42 and Rho in J774 cells, primary macrophages and osteoclasts, which parallels the rate of accumulation of unprenylated small GTPases. This effect also occurs with other inhibitors of prenylation of Rho-family proteins, such as mevastatin and GGTI-298. Furthermore, the GTP-Rac that increases after N-BP treatment is exclusively in the unprenylated form and is newly translated, since the increase in GTP-Rac can be blocked with cycloheximide. This unprenylated GTP-Rac still appears capable of activating the downstream effector PAK in J774 cell membranes. p38 MAPK, a downstream effector of PAK, is also activated by N-BPs, again dependent upon inhibition of prenylation. However, since the p38 inhibitor SB203580 enhances N-BP-induced apoptosis in J774 cells, it appears that p38 activation partially suppresses the pro-apoptotic effect of N-BPs. In conclusion, N-BP drugs probably disrupt the function of osteoclasts in vivo and other cell types in vitro by causing inappropriate and sustained activation, rather than inhibition, of some small GTPases and their downstream signalling pathways.