## Links between cell proliferation and K channel activity

*M.L. Day, Department of Physiology, University of Sydney, NSW 2006, Australia.*

Changes in the activity of potassium channels are required for proliferation of a wide variety of cell types. Pharmacological inhibition of $K^+$ channel activity can cause cell cycle arrest. Our studies on the regulation of ion channels during pre-implantation development of the mouse embryo have provided some insight into the mechanisms linking channel activity to the cell cycle. Using the patch-clamp technique, we have shown that the activity of a large-conductance $K^+$ channel in the early mouse embryo is regulated by the cell cycle (Day *et al.*, 1993). This $K^+$ channel is active during M and G1 phases and inactive during S and G2 phases. In parallel with the changes in $K^+$ channel activity there are changes in cell membrane potential such that the membrane potential is hyperpolarised when the channel is active.

The activation of this $K^+$ channel at the G2/M transition of early embryonic cell cycles does not depend on the activation of the mitotic kinase, Cdk1, and does not require the presence of the nucleus (Day *et al.*, 1998a). Thus it appears that a cytoplasmic cell cycle is functional in the early mouse embryo to regulate $K^+$ channel activity. This cytoplasmic clock is, however, not completely uninfluenced by the nuclear cell cycle clock since inactivation of the channel as the cell cycle exits M phase is affected by Cyclin B/Cdk1 activity, and inhibition of DNA synthesis prevents the decrease in channel activity that normally occurs at the G1-S transition. Thus, the $K^+$ channel in the early mouse embryo is controlled both by nuclear and cytoplasmic clocks.

Several roles for $K^+$ channels in cell proliferation have been proposed. For example, a change in $K^+$ channel activity can cause a change in cell membrane potential that can then alter the activity of other voltage-gated ion channels, such as $Ca^{2+}$ channels. In the case of the $K^+$ channel in the embryo, this role is possible since we have observed not only parallel variations in membrane potential but also cell cycle-dependent changes in the amplitude of a T-type $Ca^{2+}$ current (Day *et al.*, 1998b). A second, possible role for the $K^+$ channel in the embryo is in cell volume homeostasis. There is some evidence for this possibility since a cell swelling-induced Cl current is regulated by the cell cycle in mouse embryos being inactive during metaphase of mitosis in the 2-cell embryo at a time when the $K^+$ channel is also active (Kolajova *et al.*, 2001).

Day, M.L., Pickering, S.J., Johnson, M.H. & Cook, D.I. (1993) *Nature,* **365**: 560-562.

Day, M.L., Johnson, M.H. & Cook D.I. (1998a) *EMBO Journal,* **17**: 1952-1960.

Day, M.L., Johnson, M.H. & Cook D.I. (1998b) *Pflügers Archiv European Journal of Physiology,* **436**: 834-842.

Kolajova, M., Hammer, M., Collins, J. & Baltz, J. (2001) *Development,* **128**: 3427-3434.