substrate. Indeed, the authors show that imatinib inhibits the efflux of mitoxantrone, indicating that combined treatment with imatinib and another BCRP substrate might improve the biological availability of these drugs and/or increase the side effects due to increased cellular accumulation.

Burger and colleagues conclude that BCRP is likely to be involved in the resistance mechanisms seen in patients on long-term imatinib and indicate that future regimens for combined drug-treatment programmes should target multiple drug-resistance pathways.

Nicola McCarthy

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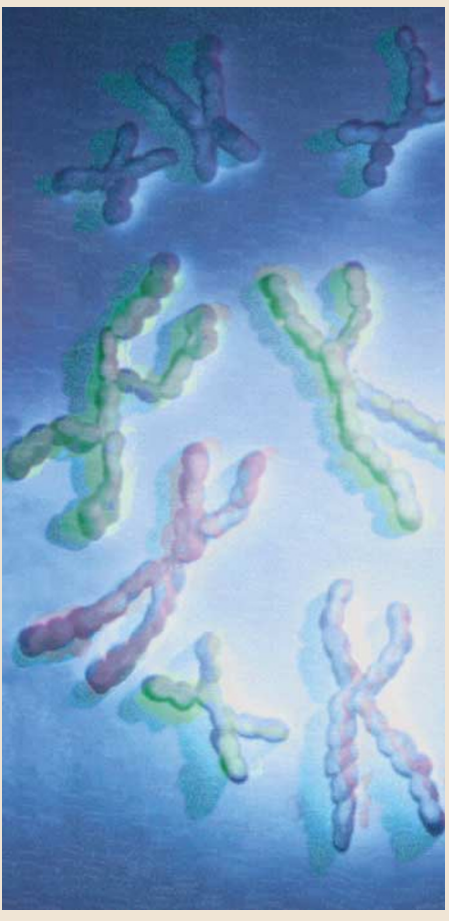

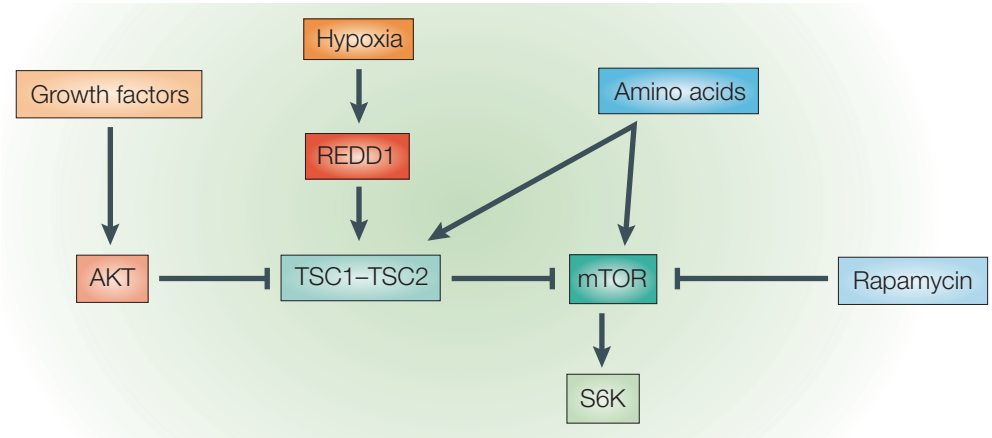

PROTEIN KINASES

REDD or dead?

Hypoxia-induced inactivation of the protein kinase mammalian target of rapamycin (mTOR) is dominant over mTOR-activating signals from growth factors and nutrients, but the functional pathway is unknown. William Kaelin and colleagues, and Jan Reiling and Ernst Hafen have now mapped this pathway using both mammalian and *Drosophila* models and show that the hypoxia-induced gene *REDD1* is required.

mTOR is regulated by a range of upstream proteins including the TSC1–TSC2 complex, which is mutated in patients with the cancer-predisposing syndrome Tuberous sclerosis. Kaelin, Brugarolas and co-workers used *Tsc2*-wild-type (*Tsc2*$^{+/+}$) or *Tsc2*-null (*Tsc2*$^{-/-}$) mouse embryo fibroblasts (MEFs) to study the effects of hypoxia on mTOR, using phosphorylation of the mTOR target protein S6 kinase (S6K) as a marker of mTOR activity. *Tsc2*$^{+/+}$ MEFs showed decreased S6K phosphorylation in response to hypoxia, as expected, but *Tsc2*$^{-/-}$ MEFs did not, indicating that a functional TSC1–TSC2 complex is required. Hypoxia-inducible factor-1α (HIF1α) expression is also regulated through mTOR and is normally downregulated in response to prolonged hypoxic conditions. However, HIF1α levels remain high in *Tsc2*$^{-/-}$ MEFs and this can be reversed by the mTOR inhibitor rapamycin, indicating that mTOR regulates HIF1α in hypoxic conditions. In addition, *Tsc2*$^{-/-}$ MEFs have a proliferative advantage over *Tsc2*$^{+/+}$ MEFs in hypoxic conditions, indicating that a failure to downregulate mTOR might contribute to tumour formation in patients with Tuberous sclerosis.

Next, Kaelin and colleagues asked if this pathway requires *de novo* mRNA synthesis and found that globally inhibiting transcription blocked the hypoxia-induced downregulation of S6K phosphorylation. *REDD1* is a HIF target gene transcribed in response to hypoxia and DNA damage, and results from Hafen's laboratory indicated that *REDD1 Drosophila* orthologues might function in the TOR pathway. So Kaelin and colleagues, in collaboration with Hafen and Reiling, examined the mTOR response in *Redd1*$^{-/-}$ MEFs. These cells do not downregulate S6K phosphorylation in response to hypoxia, so mTOR remains active but, S6K phosphorylation is downregulated in response to the exogenous expression of REDD1. Small interfering RNA experiments established that REDD1 requires TSC2 to inhibit mTOR under hypoxic conditions and are consistent with REDD1 acting upstream of the TSC1–TSC2 complex, which in turn inhibits mTOR as shown in the figure.

These findings support those of Hafen and Reiling in *Drosophila*, where the *REDD1* orthologues *scylla* and *charybdis* were identified in a screen for suppressors of AKT function, which acts upstream of TSC in the TOR pathway. Like REDD1, Scylla and Charybdis are induced by hypoxic conditions, *scylla* being a direct target of *Drosophila* HIF1. Moreover, complex genetic experiments carried out by Reiling and Hafen show that Scylla and Charybdis act downstream of AKT, but upstream of TSC to regulate TOR and S6K activity.

Overall, these results indicate that inhibition of the mTOR pathway by hypoxia is likely to be important for tumour inhibition. Whether *REDD1* is mutated in human tumours is as yet unclear, but these results indicate that *REDD1* might function as a tumour-suppressor gene.

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References and links

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