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THERAPY

Swings and roundabouts

> “the treatment of mice with *Nf1*-deficient AML with the MEK inhibitors initially prolonged survival”

Children with neurofibromatosis type 1 are heterozygous for *NF1* and have a substantially increased risk of developing an aggressive myeloproliferative disorder (MPD): juvenile myelomonocytic leukaemia (JMML). Using mouse models, Jennifer Lauchle, Kevin Shannon and colleagues have identified the stages of this disease that might be amenable to treatment with drugs that target the RAF–MEK–ERK signalling pathway.

NF1 encodes a GTPase-activating protein that negatively regulates the activity of Ras, and tumours that arise in patients with neurofibromatosis type 1 have frequently lost the remaining normal allele. Specific deletion of *Nf1* in bone marrow cells in mice leads to the development of an MPD that is similar to JMML. As JMML can progress to acute myeloid leukaemia (AML), Lauchle and colleagues used retroviral insertional mutagenesis in newborn mice to identify mutations that cooperate with the loss of *Nf1*. These mice rapidly developed AML.

STOCKBYTE

Bone marrow cells from patients with JMML who have lost the remaining normal *NF1* allele have increased activity of the downstream Ras effector MEK, so the authors exposed blast colonies that were explanted from *Nf1*-deficient mice with AML to small-molecule MEK inhibitors. The growth of the blast colonies was more sensitive to MEK inhibition than the growth of myeloid progenitor cells that were explanted from *Nf1*-deficient mice with MPD or that were from wild-type mice. Therefore, the progression to AML seems to increase the reliance of the leukaemia cells on MEK.

As might be expected, the treatment of mice with *Nf1*-deficient AML with the MEK inhibitors initially prolonged survival, but relapse with resistant leukaemia was common. By identifying the retroviral insertion sites, the authors found genes potentially involved in the development of resistance to MEK inhibitors. Comparison of sensitive and resistant AML cells indicated that the activation of *Rasgrp1* or the inactivation of one allele of *Mapk14* (which encodes p38α) might be involved. RasGRP proteins promote guanine nucleotide exchange on Ras, leading to higher levels of active Ras–GTP, and AML cells with an insertion close to *Rasgrp1* had increased levels of Ras–GTP that correlated with MEK resistance. Moreover, inhibition of *Rasgrp1* using short hairpin RNAs resulted in sensitivity to MEK inhibition. Similarly, a drug that inhibits p38α activity induced resistance to MEK inhibition in previously MEK inhibitor-sensitive AML cells. *Nf1*-deficient AML cells have increased expression levels of p38α, and the authors propose that inhibition of MEK leads to unopposed p38α activity — a known inducer of apoptosis. Importantly, analysis of the sensitive and resistant phases of AML in these animals indicated that resistance arose as a result of selection for previously existing resistant subclones.

These results indicate that retroviral insertional mutagenesis is a useful tool for understanding disease progression and drug resistance, as well as understanding the molecular reasons for drug sensitivity at specific stages during disease progression.

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ORIGINAL RESEARCH PAPER Lauchle, J. O. *et al.* Response and resistance to MEK inhibition in leukaemias initiated by hyperactive Ras. *Nature* 02 Sep 2009 (doi:10.1038/nature08279)