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MOUSE MODELS

Closer than you think

How closely mouse models mimic human disease and how useful they are for guiding therapeutic decisions has, to some degree, been a matter of luck. Recently, there has been a concerted effort to produce mouse models that can mirror outcomes in patients with specific types of cancer and a new mouse model of acute myeloid leukaemia (AML) seems to have passed muster.

After consulting a new dataset generated from 111 cases of paediatric AML to extract common genetic changes thought to affect patient outcome, Scott Lowe and colleagues infected mouse fetal liver cells, which contain haematopoietic stem and progenitor cells, with *Nras*^{G12D} and either *AML1–ETO9a* (*AML1* is also known as *RUNX1*) or *MLL–ENL* (*ENL* is also known as *MLLT1*). These two fusion genes are associated with a good and poor prognostic outcome, respectively, and are often associated with mutations in *NRAS*. However, the heterogeneity of AML makes it difficult to translate these associations into the clinic, so can mouse models help? The authors carefully verified that syngeneic mice transplanted with these cells developed human-like AML and worked out the best means of treating these mice with standard chemotherapy regimens used in newly diagnosed patients with AML, then asked whether these mice showed altered rates of survival after treatment. In agreement with human outcome data, the mice with *Nras*^{G12D};*AML1–ETO9a*-induced disease responded to treatment, with 20% showing no disease relapse, whereas mice with *Nras*^{G12D};*MLL–ENL* showed only a transient response to therapy.

What drives this differential response? The authors analysed *Nras*^{G12D};*AML1–ETO9a* AML cells shortly after the first course of treatment and identified 226 mRNAs that increased and 172 that decreased in response to treatment. Using KEGG pathway analysis they found that five pathways were affected by drug treatment, the most significant of which included genes involved in the p53 pathway. Importantly, *Nras*^{G12D};*MLL–ENL* cells showed little alteration in the expression of these genes after drug treatment and expressed lower levels of the p53 target gene *Cdkn1a*, implying lower baseline levels of p53 expression in these cells. Moreover, a severe attenuation of the chemotherapy-induced p53 response was evident in these cells, allowing the authors to conclude that MLL fusions blunt the p53 response. Analysis of both fusion genes in *Trp53*-null fetal liver cells injected into syngeneic mice showed that cell morphology and immunophenotype of the disease induced by *AML1–ETO9a* was unchanged in the absence of p53, but that the disease was more aggressive with a poor response to therapy. As expected, p53 loss had no significant effect on cells expressing *MLL–ENL*.

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These results are significant as they indicate that this genetically defined mouse model of AML can be used to predict responses to chemotherapy regimens in patients, despite the heterogeneity of the human disease. They also show that, in addition to the 13% of patients with AML that have *TP53* mutations, those with an MLL fusion are also likely to have an impaired p53 response. Thus, on the basis of the mouse data one would predict that these patients will have a poor response to chemotherapy and that screening for such changes might help to determine patient prognosis.

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ORIGINAL RESEARCH PAPER Zuber, J. *et al.* Mouse models of human AML accurately predict chemotherapy response. *Genes Dev.* **23**, 877–889 (2009)