TUMOUR MICROENVIRONMENT

Target practice

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The many adventures of MYC continue this month with a new publication by Laura Soucek, Gerard Evan and colleagues, which indicates that blocking the activity of endogenous LMYC, NMYC and MYC (collectively referred to as Myc) suppresses tumour development by eliciting effects both on tumour cells and on the tumour microenvironment.

Having previously shown that the systemic expression of the dominant inhibitory Myc dimerization domain mutant, Omomyc, inhibits the development of tumours in a $KRAS^{G12D}$-dependent mouse model of lung cancer, Evan and colleagues wanted to address whether the effects of Myc inhibition are exercised via the tumour cells or the surrounding cells that constitute the tumour microenvironment, and whether targeting endogenous Myc might be applicable beyond tumours that are induced by KRAS. Thus, they crossed *TRE-Omomyc*;*CMVrtTA* mice with *Rip1Tag2* mice, which progress through pancreatic hyperplasia and dysplasia to overt pancreatic β-cell tumours because of the expression of SV40 large T antigen in the β-islet cells of the pancreas. *Omomyc* is under the control of the tetracycline-responsive promoter element, allowing its expression to be turned on and off by the presence of doxycycline. Addition of doxycycline to the animals' drinking water at 7 weeks of age followed by sacrifice at 14 weeks of age showed that expression of Omomyc suppressed the development of the islet tumours that were abundant in mice not given doxycycline. Expression of Omomyc had a similar effect on the more advanced dysplastic tumours and carcinomas that are present in 11-week-old mice. Importantly, the rare individual islet tumour that did not respond to Omomyc had lost expression of this transgene and no other mechanisms of resistance were evident. So, inhibition of endogenous Myc induces the regression of tumours that are driven by the expression of the SV40 T antigen, but how?

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The dysplastic lesions are highly angiogenic and it seems that expression of Omomyc initially induces apoptosis in the endothelial cells of these lesions, followed by the tumour cells. No interaction between the angiogenic factor, vascular endothelial growth factor (VEGF), and its receptor, VEGFR2, could be found in the lesions in which Myc was inhibited, and further analyses indicated that this was primarily because the release of VEGF from the extracellular matrix by matrix metalloproteinases was reduced owing to the absence of macrophages and neutrophils that are normally recruited to these lesions. All of these findings point to the plausible conclusion that the therapeutic effect of Omomyc is primarily in the tumour microenvironment. However, expression of Omomyc exclusively in the pancreatic β-tumour cells induced the same collapse of the tumour microenvironment, indicating that Myc expression in the tumour cells is required to maintain the tumour microenvironment and it is this interaction that Omomyc interferes with.

So, targeting Myc remains a viable proposition in principle. In practice, it is not yet clear precisely which functions of MYC need to be blocked to induce tumour regression and whether a Myc-targeted drug will need to inhibit all three MYC proteins, as Omomyc does, in order to avoid the evolution of resistance.

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ORIGINAL RESEARCH PAPER Sodir, N. M. *et al.* Endogenous Myc maintains the tumour microenvironment. *Genes & Dev.* 8 Apr 2011 (doi:10.1101/gad.2038411)