TUMORIGENESIS

# Decidedly different

**DOI:**
10.1038/nrc1981

**URLs**

BCL-XL
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=598

MYC
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=4609

ARF (CDKN2A locus)
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=1029

p53
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=7157

*Puma*
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=27113

*Noxa*
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=5366

*BAX*
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=581

The aberrant expression of oncogenes induces tumour development, but it also triggers apoptosis or cell-cycle arrest. So, cooperating mutations are needed to overcome these barriers, but which is more cooperative: loss of apoptosis or loss of cell-cycle arrest?

Previous work from Gerard Evan's group has shown that the activation of a regulatable form of the MYC protein (MYC–$ER^{TAM}$) in the insulin-secreting β-islet cells (β-cells) of the pancreas (*pIns–Myc–$ER^{TAM}$* mice) results in the apoptosis of these cells. Inhibiting MYC-induced apoptosis through the expression of the anti-apoptotic protein BCL-$X_L$ results in an increase in β-cell numbers.

Other mutations, such as the loss of the tumour suppressors ARF or p53 also cooperate with MYC, but do they also work by suppressing MYC-induced apoptosis? Evan's group crossed the *pIns–Myc–$ER^{TAM}$* mice with *$Arf^{-/-}$* or *$Trp53^{-/-}$* mice. Surprisingly, the β-cells of the *pIns–Myc–$ER^{TAM}$/$Arf^{-/-}$* mice had higher rates of MYC-induced apoptosis than *pIns–Myc–$ER^{TAM}$* mice, and higher rates of proliferation than the β-cells that expressed both MYC–$ER^{TAM}$ and BCL-$X_L$. However, this increased proliferation in the *pIns–Myc–$ER^{TAM}$/$Arf^{-/-}$* mice did not cause an expansion of the β-cell population owing to the high levels of apoptosis. β-cells from the *pIns–Myc–$ER^{TAM}$/$Trp53^{-/-}$* mice showed an increased rate of proliferation similar to the *pIns–Myc–$ER^{TAM}$/$Arf^{-/-}$* mice, but rates of apoptosis were lower in this case than in *pIns–Myc–$ER^{TAM}$* mice.

The aberrant expression of MYC normally induces the expression of ARF, which leads to the stabilization of p53, expression of the anti-proliferative, cyclin-dependent-kinase inhibitor p21 and the induction of apoptosis. The expression of p21 does not occur in the *Arf* or *Trp53* knockout cells, which leaves MYC-induced proliferation unchecked, but apoptosis is not affected. These data imply several important points. First, that ARF limits the oncogenicity of MYC by inhibiting proliferation; second, that this is p53 dependent; and third, that ARF does not limit the oncogenicity of MYC by inducing apoptosis. The lack of p21 expression also explains the increased proliferation in the *pIns–Myc–$ER^{TAM}$/$Trp53^{-/-}$* mice. The authors suggest that MYC-induced apoptosis is partially inhibited in the p53-deficient mice because p53 is directly involved in inducing apoptosis by upregulating the expression of pro-apoptotic genes such as *Puma*, *Noxa* and *BAX*.

As ARF loss cooperates with MYC by increasing proliferation, and BCL-$X_L$ cooperates by suppressing MYC-induced apoptosis, will the combination of ARF loss and BCL-$X_L$ expression further increase the oncogenicity of MYC? When MYC was activated, *pIns–Myc–$ER^{TAM}$/RIP7–Bcl-$x_L$/$Arf^{-/-}$* mice rapidly developed invasive tumours in which apoptosis was suppressed. Because MYC-induced apoptosis is partially suppressed in the p53-deficient background, *pIns–Myc–$ER^{TAM}$/$Trp53^{-/-}$* mice also develop invasive tumours. However, the tumours remain histologically

different — there is no apoptosis in the tumours of *pIns–Myc–$ER^{TAM}$/RIP7–Bcl-$x_L$/$Arf^{-/-}$* mice, but apoptosis persists in the tumours of *pIns–Myc–$ER^{TAM}$/$Trp53^{-/-}$* mice.

These results increase our understanding of how these pathways synergize in mouse models, but the relative importance of suppression of apoptosis and further increased proliferation is still unclear in the evolution and protracted development of human tumours.

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**ORIGINAL RESEARCH PAPER** Finch, A. *et al.* Bcl-$x_L$ gain of function and *p19$^{ARF}$* loss of function cooperate oncogenically with Myc *in vivo* by distinct mechanisms. *Cancer Cell* **10**, 113–130 (2006)
**FURTHER READING** Pelengaris, S., Khan, M. & Evan, G. c-MYC: more than just a matter of life and death. *Nature Rev. Cancer* **2**, 764–776 (2002)