1. Nasmyth, K. & Schleifer, A. *Phil. Trans. R. Soc. B* **359,** 99–108 (2004).
2. Tinker-Kulberg, R.L. & Morgan, D.O. *Genes Dev.* **13,** 1936–1949 (1999).
3. Stegmeier, F., Visintin, R. & Amon, A. *Cell* **108,** 207–220 (2002).
4. Sullivan, M. & Uhlmann, F. *Nature Cell Biol.* **5,** 249–254 (2003).
5. Papi, M., Berdougo, E., Randall, C.L., Ganguly, S. & Jallepalli, P.V. *Nature Cell Biol.* **7,** 1029–1035 (2005).
6. Uhlmann, F., Wernic, D., Poupart, M.-A., Koonin, E.V. & Nasmyth, K. *Cell* **103,** 375–386 (2000).
7. Waizenegger, I.C., Hauf, S., Meinke, A. & Peters, J.-M. *Cell* **103,** 399–410 (2000).
8. Hauf, S., Waizenegger, I.C. & Peters, J.-M. *Science* **293,** 1320–1323 (2001).
9. Siomos, M.F. *et al. Curr. Biol.* **11,** 1825–1835 (2001).
10. Zou, H., Stemmann, O., Anderson, J.S., Mann, M. & Kirschner, M.W. *FEBS Lett.* **528,** 246–250 (2002).
11. Viadiu, H., Stemmann, O., Kirschner, M. & Walz, T. *Nature Struct. Mol. Biol.* **12,** 552–553 (2005).
12. Herzig, A., Lehner, C.F. & Heidmann, S. *Genes Dev.* **16,** 2443–2454 (2002).
13. Giménez-Abián, J.F., Díaz-Martínez, L.A., Waizenegger, I.C., Giménez-Martín, G. & Clarke, D.J. *Cell Cycle* **4,** (submitted); preprint at <http://www.landesbioscience.com/journals/cc/abstract.php?id=2147 (2005).
14. Pandey, R., Heidmann, S. & Lehner, C.F. *J. Cell Sci.* **118,** 733–742 (2005).
15. Funabiki, H., Kumada, K. & Yanagida, M. *EMBO J.* **15,** 6617–6628 (1996).
16. Gorr, I.H., Boos, D. & Stemmann, O. *Mol. Cell* **19,** 135–141 (2005).

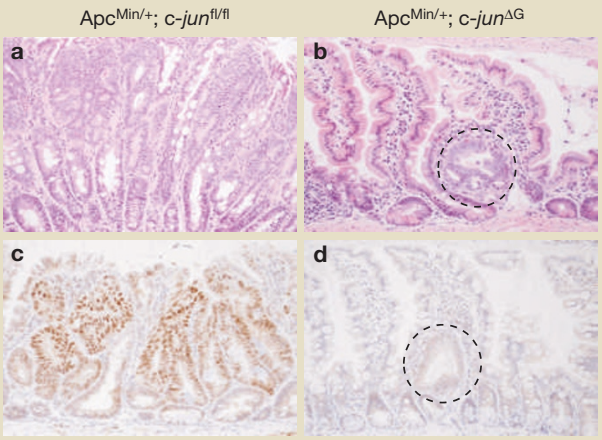
Tumorigenesis: TCF4 feeds c-Jun

Mutations in the canonical Wnt pathway proteins APC or β-catenin, which often result in constitutive activation of the transcription factor TCF4, are a frequent occurrence in colorectal cancers. Nateri *et al.* now report (*Nature* **437,** 281; 2005) that canonical Wnt signalling joins forces with a non-canonical Wnt pathway — acting through JNK — to exacerbate Wnt's contribution to gut tumorigenesis.

The authors identified TCF4 to be a binding partner of phosphorylated c-Jun — a component of the AP-1 transcription factor — using a genetic screen in yeast. They confirmed the c-Jun–TCF4 interaction biochemically, and showed that c-Jun and TCF4 form a ternary complex with β-catenin. JNK stimulates activation of c-Jun, and phosphorylation of c-Jun results in the increased transcriptional activation of several target genes, including c-*jun*. Chromatin immunoprecipitation analysis of the native c-*jun* promoter revealed that binding of c-Jun and β-catenin–TCF4 to this promoter is dependent on JNK activity.

So is there crosstalk between JNK and the canonical Wnt pathway? c-Jun and TCF4 cooperate in the induction of c-*jun* activity and this requires both the TCF and AP-1 sites of the c-*jun* promoter acting *in cis*, and depends on amino-terminal c-Jun serine residue phosphorylation. Furthermore, when the authors knocked down β-catenin expression by siRNA, they observed a reduction in the transcriptional activation of c-*jun* by c-Jun–TCF4, suggesting that β-catenin was required for the activation of the c-*jun* promoter by these transcription factors.

To test the physiological relevance of the c-Jun–TCF4 interaction, Nateri *et al.* crossed mice heterozygous for the Apc^{Min} mutation, which causes intestinal tumours by activating TCF4/β-catenin, with mice expressing a mutant form of c-Jun that cannot bind TCF4. The lifespan of these compound mutant mice was extended compared with wild-type controls, and the average size of their adenomas was reduced. Furthermore, when Apc^{Min} heterozygous mice were bred with transgenic mice that had lost c-Jun expression specifically in the gut, tumours did not develop until nine months of age. Thus, it appears that β-catenin signalling was no longer able to induce tumour formation in the absence of c-Jun, and suggests that c-Jun repression protects Apc^{Min} heterozygous mice against the development of intestinal tumours.



$Apc^{Min/+}$ mice display numerous large intestinal adenomas (**a**, **c**), whereas mice that have lost c-Jun expression ($Apc^{Min/+}$;c-$jun^{\Delta G}$) in the gut (**b**, **d**) are characterized by the presence of cysts (dashed circle). (**c**, **d**) Intestinal sections stained for c-Jun.

Collectively, the findings by Nateri *et al.* point to a mechanism whereby the interaction between TCF4 and phospho-c-Jun controls the transcriptional activation of c-*jun* by recruiting β-catenin. JNK inhibitors have proven successful in *in vivo* models of neurodegeneration, and the c-Jun–TCF4 interaction should help to invigorate effective therapeutic targeting of c-Jun-related diseases, including colon cancers.

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