which there is partial EST coverage, contains further leucine repeats. The size of PCR-amplified products (from a *C. elegans* cDNA library) is consistent with these data.

Could *C. elegans* express other components of Toll pathways? A key element of Toll signal transduction are the kinases recruited to IL-1R sequences[8] by adapters. The IRAK-1 and -2 kinases play this role in *Homo sapiens*, whilst the *Drosophila* equivalent is Pelle. BLAST searches allowed us to identify a *C. elegans* gene encoding a protein that is 35% identical to Pelle. We then went on to identify a worm homologue of Pellino, a protein that associates with the kinase domain of Pelle. *C. elegans*-Pellino shares 41% sequence homology with its *Drosophila* homologue (Fig. 1). Such sequence similarities leave us in no doubt that these are the worm versions of *Drosophila* Pelle and Pellino. We retrieved ESTs for Pellino, demonstrating that it is expressed, and PCR has confirmed this. Toll signals mobilize the Rel and NF-κB family of transcription factors. So far, these proteins appear to be absent from *C. elegans*, leaving its Toll-like pathway uncoupled from a nuclear readout. However, the recent cloning of a *C. elegans* TNF receptor-associated factor (TRAF) provides an alternative route to the nucleus[9]. In this scenario, *C. elegans* would use TRAF to activate the JNK pathway in a similar fashion to that described for mammalian cells[10]. It now becomes questionable as to whether *C. elegans* 'lost' its Rel-like transcription factors or whether it simply never needed them. Future work will tell us the extent to which these genes are employed in development versus immunity in nematodes. Either way, a more detailed study of these genes will help us to understand what they are doing in the worm and perhaps tell us when a patterning pathway turned to defence, or vice-versa.

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*Fhit*ness and cancer in the mouse

The human *FHIT* gene is located at 3p14.2, a position on the short arm of chromosome 3 that includes the most fragile site in the human genome and spans a t(3;8) translocation that predisposes to early onset, clear cell renal carcinoma. *FHIT* deletions are extremely common in human cancers, especially those that arise from lung and stomach epithelia exposed to environmental carcinogens. Nonetheless, because *FHIT* spans a fragile site and tumors usually lose *FHIT* by deletion rather than point mutation, some researchers have argued that *FHIT* deletions are not a cause of cancer but rather a consequence of genome instability. Although the early kinetics of *FHIT* inactivation in lung carcinogenesis, and the fact that re-expression of *Fhit* protein induces apoptosis in parallel with suppressing tumor formation, support assignment of *FHIT* as a tumor suppressor, many cancer geneticists consider the knockout mouse to be the ultimate test.

If *FHIT* inactivation in humans is merely a consequence of genome instability, then inactivation of *Fhit* in the mouse would not be expected to effect carcinogenesis. On the other hand, if *FHIT* loss in humans does contribute to cell transformation, then murine *Fhit*$^-$ animals might be expected to develop tumors, potentially in the same organs in which human *FHIT*$^-$ tumors appear. This was precisely the result obtained by Fong *et al.*[1], all the more striking because this was after genetically inactivating only one *Fhit* allele in the mouse. Because the murine *Fhit* locus, like its syntenic human counterpart, is fragile, mice that were heterozygous for inactivation of *Fhit* developed stomach and sebaceous tumors when given N-nitrosomethylbenzylamine intragastrically. Ten weeks after treatment, 10 of 12 heterozygous mice had tumors of the forestomach, and 7 of 12 had sebaceous tumors; these tumors lacked Fhit protein. Among eight identically treated wild-type mice, one developed a tumor in the forestomach and none developed a sebaceous tumor. The combination of visceral and sebaceous tumors in *Fhit* heterozygous mice struck these researchers as similar to human Muir–Torre syndrome (MTS), a variant of hereditary nonpolyposis colorectal cancer, and they showed that some human MTS tumors are Fhit.

Whereas MTS usually arises from inherited defects in mismatch repair genes, the full complement of genetic changes in MTS tumors is not known. The phenotype of *Fhit* heterozygous mice not only demonstrates that loss of *Fhit* predisposes to carcinogenesis, but also suggests that an intact mismatch repair system might either protect the *FHIT* locus or maintain Fhit expression in humans.

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