WEB WATCH

- http://www.pancreatica.org

Realistic goals

Pancreatic cancer has the lowest survival rate of any solid tumour. Although it might be cold comfort to those living with the disease that there is a web site just for them, Pancreatica works well because it's realistic about the chances of a cure and because it isn't over-ambitious. The site provides only four main resources, but each is carefully thought out and regularly updated. And although it's designed with patients in mind, researchers will find much to enlighten them here.

The most prominent resource is a searchable database of clinical trials. The search page is carefully structured so that the user can select features such as cancer type, trial phase and type of treatment from pull-down menus, as well as searching according to trial locations and whether prior therapy is allowed.

Pancreatic cancer news provides press releases on basic and clinical research. There's also a 'newswire service', providing relevant newspaper articles. There's some overlap in content between this and the news page, and researchers would probably find the former the most useful of the two.

The 'frequently asked questions' section provides clear summaries on 15 questions, spanning diagnosis to end-of-life issues. Controversies, such as the lack of an internationally recognized grading and staging system, are discussed, and hypertext links to other sites are provided.

Pancreatica also provides a list of links and research resources; researchers will find the lists of institutions and charities that fund research into pancreatic cancer valuable. The site provides a sober reminder of why we're doing cancer research, and its producers should be congratulated for their measured approach to a challenging topic.

Cath Brooksbank

APOPTOSIS

The p53 mafia

At the heart of a report in *Nature* lies a tale of drugs and violent death. The leading role in this story goes to p53, which orders the apoptotic execution of cells in response to DNA-damaging agents such as doxorubicin. But as Elsa Flores, Tyler Jacks and co-workers now show, this is a family affair — for p53 needs its close relatives p63 and p73 to carry out the task.

The structural and functional similarities between p53 and its relatives led Jacks and colleagues to ask whether p63 and p73 are involved in the p53-dependent response to DNA-damaging agents. They studied this using mouse embryo fibroblasts (MEFs) that had been sensitized to undergo apoptosis by expression of the *E1A* oncogene and were deficient in various p53 family members.

As expected, after treatment with doxorubicin, the *Trp53*$^{-/-}$ MEFs were resistant to apoptotic death. The *Trp63*$^{-/-}$ and *Trp73*$^{-/-}$ cells showed only a partial resistance to apoptosis, but MEFs that lacked both of these genes were as resistant to apoptosis as were the *Trp53*$^{-/-}$ cells. Moreover, cells that lacked p53/p63 or p53/p73 were more resistant than MEFs that

LEUKAEMIA

Common ground

Scattered evidence has implicated the Notch family — a group of receptors that are involved in cell-fate choices — in the development of T-cell acute lymphoblastic leukaemia (T-ALL). But whether Notch dysregulation is a general rule in these leukaemias, and how it might contribute to neoplasia, has remained a mystery, especially as T-ALL is a diverse disease that is characterized by a range of different cytogenetic changes. Could a single signalling defect unify this mixed bag? Diana Bellavia and colleagues now identify a molecule that seems to collaborate with Notch to cause T-ALL, and might be a global marker for the disease.

The same group previously generated a mouse model of T-ALL by overexpressing a truncated, constitutively active Notch3 mutant (Notch3-IC) in thymocytes (T-cell precursors). The leukaemic cells expressed pTα, a component of the pre-T-cell receptor that enhances thymocyte survival and proliferation in the absence of an antigenic stimulus. Might human T-ALL cells also express pTα? Reverse transcriptase polymerase chain reaction and northern blot analysis of 30 T-ALL cases revealed that Notch3 and pTα were expressed in all cases examined. HES1, a transcription factor that is downstream of Notch signalling, was also expressed in T-ALL cells. By contrast, normal peripheral T cells expressed none of these transcripts. Notch3 and pTα expression also decreased to undetectable levels in T-ALL that was in remission.

So is pTα expression necessary for lymphomagenesis? To investigate this, the authors crossed their Notch3-IC mice with pTα$^{-/-}$ mice. Notch3-IC mice with one or two copies of pTα all developed T-cell tumours, whereas only 10% of Notch3-IC, pTα$^{-/-}$ mice developed tumours. This was not due to an inability of pTα$^{-/-}$ thymocytes to develop properly, as the number of mature peripheral T cells was almost normal in these mice.

So expression of Notch3 and pTα seems to be a common thread in all cases of T-ALL, regardless of developmental stage or karyotype. Whether Notch3 provides the signal that sustains pTα expression is an intriguing question for the future.

Cath Brooksbank

References and links

ORIGINAL RESEARCH PAPER Bellavia, D. *et al.* Combined expression of pTα and Notch3 in T cell leukemia identifies the requirement of preTCR for leukemogenesis. *Proc. Natl Acad. Sci. USA* **99**, 3788–3793 (2002)

FURTHER READING Bellavia, D. *et al.* Constitutive activation of NF-κB and T-cell leukemia/lymphoma in Notch3 transgenic mice. *EMBO J.* **19**, 3337–3348 (2000)