Cancer

Cell survival guide

Eric R. Fearon and Kathleen R. Cho

A jaded observer might consider the cancer research field near maturity and surprising new results improbable. But work on the protein netrin-1 shows that unforeseen insights into cancer can still occur.

Named from the Sanskrit word for 'one who guides', the netrin-1 protein was discovered because of its ability to direct the migration of axons in the developing spinal cord[1,2]. The functions of netrin proteins in axon guidance and neural cell migration have consequently received much attention (reviewed in ref. 3). But the report on page 80 of this issue from Mazelin *et al.*[4] makes the case that netrin-1 might offer unanticipated guidance for the cancer field as well.

Netrins are secreted proteins that act on neural cells through transmembrane receptors of the DCC and UNC5H families (reviewed in ref. 3). DCC stands for 'deleted in colorectal carcinomas', and as its name implies, *DCC* was initially described as a candidate tumour-suppressor gene. In colorectal cancer, a chromosomal region containing *DCC* is frequently deleted. This is often accompanied by low or absent expression of the DCC protein and, occasionally, by specific *DCC* mutations[3,5,6] — as expected for a tumour-suppressor gene. However, it has been argued that *DCC* might not actually be a tumour-suppressor gene, but be functioning only in the nervous system[7,8]. This point of view is based on the fact that the mechanisms underlying reduced or absent *DCC* expression in most cancers are poorly defined[3,5,6], and the observation that mice lacking one copy of *Dcc* do not have an obvious predisposition to tumours[7].

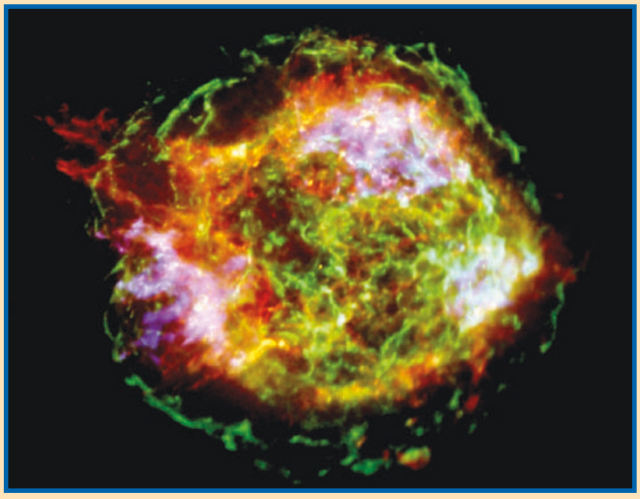
The three *UNC5H* genes — *UNC5H1*, *UNC5H2* and *UNC5H3* — are also proposed to be tumour-suppressor genes[9]. But concerns similar to those for *DCC* could be raised about the evidence that links defects in the *UNC5H* genes to cancer in humans. Possible mechanisms contributing to the loss of *UNC5H* gene expression in cancer include deletion or mutation of *UNC5H* genes, and transcriptional mechanisms[9]. For instance, the *UNC5H2* gene is regulated by the p53 tumour-suppressor protein[10], and p53 function is often defective in cancer.

Perhaps the strongest suggestion that *DCC* and *UNC5H* are indeed involved in cancer comes from observations that, in cultured cells, the DCC and UNC5H proteins promote cell death when netrin-1 is absent but enhance cell survival when netrin-1 is present[3,11,12]. This behaviour is consistent with the hypothesis that DCC and UNC5H belong to a class of cellular receptor called dependence receptors, which induce programmed cell death unless they are occupied by their ligand. Theoretically, there are two mechanisms by which such receptors might cause cancer: either the ligand is present in excess or in the wrong location, so that inappropriate cell survival is encouraged; or the receptors are inactivated or deleted somehow so that cell death is no longer promoted when there is little or no ligand. The specific mechanisms by which netrin-1 binding to DCC or UNC5H affects cell survival or death remain unknown, but Mazelin and colleagues[4] set out to test the dependence-receptor hypothesis *in vivo*.

They genetically engineered mice to express netrin-1 in epithelial cells in those parts of the intestinal lining where it is not normally expressed. As expected, they saw a reduction in cell death in small intestine and colon tissues. More notably, they found that these mice tended to develop spontaneous pre-cancerous intestinal epithelial growths (adenomas), with 17% of netrin-1 transgenic mice developing at least one adenoma, whereas control mice had none. Mice carrying constitutive mutations in the *Apc* (*adenomatous polyposis coli*) gene are well known to develop intestinal adenomas. Thus, to test the tumour-promoting effects of netrin-1 further, Mazelin *et al.* studied mice carrying the *Apc* gene defect together with the netrin-1 transgene. Compared with mice having just the *Apc* defect, mice carrying both the transgene and the defect had many more 'high-grade' adenomas or lesions with markedly aberrant cellular and glandular morphology. What's more, about 50% of

Astronomy

The quiet one



NASA/CXC/GSFC/U. HWANG *ET AL.*

No one noticed the death of Cassiopeia A. But this star's supernova remnant, the youngest known in the Milky Way, has since become an icon of the success of the Chandra X-ray Observatory. Chandra produced its first images of Cassiopeia A in 1999, soon after its launch. Five years later, these images have become exquisite in their detail.

From the size and rate of expansion of the remnant, it is estimated that the light from Cassiopeia A's supernova explosion reached Earth more than 300 years ago. Over the course of history, firm sightings of other supernovae have been made, noted by contemporary astronomers as 'new stars' in the sky. Cassiopeia A, it seems, might have been spotted only by John Flamsteed, Britain's first Astronomer Royal. In 1680, he recorded a star close to Cassiopeia A's position — but subsequent star catalogues have tended to regard this as an error. Anyway, an explosion date in the 1660s would fit with the observed expansion better.

In all likelihood, Cassiopeia A just wasn't very bright on the supernova scale of things. But at radio wavelengths, it is now the brightest object in the sky. And in the X-ray emission picked up by Chandra, details of Cassiopeia A's structure and composition are clear. The shock wave created by the supernova (the outer green ring in this picture) now spans a diameter of 10 light years; bipolar jets of mostly silicon atoms (one of which can be seen, in red, on the upper left) suggest that such a feature might be more common in supernovae than had been thought.

The tiny yellow speck at the centre of this 1-million-second exposure is a neutron star — an incredibly dense mass of collapsed stellar material formed from the supernova. Cassiopeia A's neutron star is strangely quiet: it is not firing out pulses of radiation as other neutron stars do. The Chandra team suspects that this star might have a particularly strong magnetic field, even qualifying as a 'magnetar' — a class of neutron stars with magnetic fields a thousand trillion times stronger than Earth's. **Alison Wright**

100 YEARS AGO

The value and possibilities of wireless telegraphy as a journalistic adjunct are described in Saturday's *Times* by the special correspondent who established a wireless telegraph system at the theatre of war operations in the Far East with such success that both the belligerents regarded the enterprise as dangerous to their interests. The Japanese Government placed such limitations upon the free movements of the *Haimun* — the vessel chartered by the *Times* for its wireless telegraph service — that this means of communication was discontinued of necessity; and there seems little doubt that in future the use of all systems of wireless communication will be controlled by international law.

From *Nature* 1 September 1904.

50 YEARS AGO

A New Periodic Table of the Elements Based on the Structure of the Atom. **To demonstrate the periodicity in the properties of the chemical elements, Lothar Meyer chose the most direct representation: he plotted the elements in the order of their atomic weights on the abscissa, and the values of the property in question on the ordinate. At the same time, Mendeléef published the Periodic Law in the form of tables… During the following decades innumerable attempts were made to improve on Meyer and Mendeléef. All sorts of representations, trees with branches, concentric circles, spirals, figure-eights, and various three-dimensioned curves were tried;…behind all this was the hope to get nearer to the mystery of the periodic system if a more perfect arrangement could be found. But the scientific result of all these attempts was nil… It is somewhat astonishing to see that quite recently "A New Periodic Table of the Elements" has been published which is a revival of the old discarded attempts. The curves, for example, which represent the specific gravity of the elements, are based on one of the well-tried spirals and can, naturally, not avoid the old drawbacks… The author recommends even a cone-shaped periodic chart, another repetition of previous suggestions; whoever takes the trouble to follow the advice to cut the drawing out and to gum it together as a cone, will scarcely get any insight into the sequence of chemical elements which the usual tables do not give.**

From *Nature* 4 September 1954.

high-grade adenomas in mice carrying the transgene and the *Apc* defect contained foci of invasive carcinoma, whereas no carcinomas were seen in mice with only the *Apc* defect.

In the normal small intestine and colon, epithelial cells proliferate predominantly in the bottom of small pits called crypts, before becoming specialized and migrating upwards, where cells die and slough off (Fig. 1). In normal mice, Mazelin *et al.* found that *Dcc* was uniformly expressed throughout the intestinal epithelium, whereas netrin-1 expression was mostly restricted to the base of the crypts. This is consistent with the view that interaction of netrin-1 with its receptors might regulate survival versus cell death, with netrin-1 stimulating proliferation in the crypt and the absence of netrin-1 perhaps contributing to cell death at the surface.

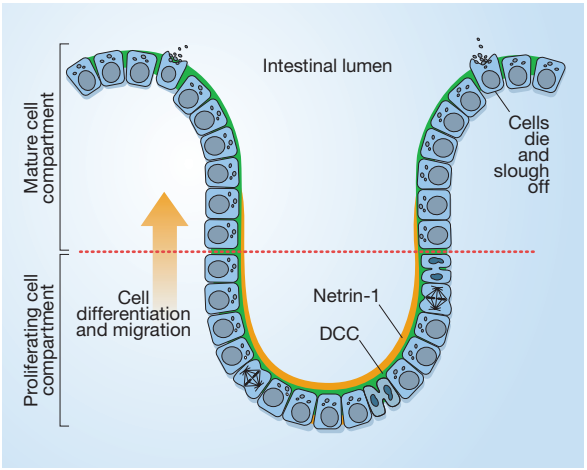


Figure 1 **Model for the role of netrin-1 and DCC in regulating cell survival and death in the intestine, based on Mazelin and colleagues' results[4]. In a normal intestine, cells proliferate at the bottom of pits called crypts. They then migrate upwards towards the surface. As they go, the cells stop proliferating, become more specialized, and ultimately die. Netrin-1 expression is mostly restricted to the base of the crypt, but expression of its receptor DCC is essentially uniform in all epithelial cells[4]. According to the dependence-receptor hypothesis, the findings imply that binding of netrin-1 to DCC might contribute to cell survival in the crypt. At the surface, the absence of netrin-1 leads to DCC-mediated cell death.**

With this paper, Mazelin *et al.* offer encouraging *in vivo* data to support the hypothesis that the DCC and UNC5H proteins function as dependence receptors for netrin-1. Yet there are some caveats. First, because there are other netrin-1 receptors[13,14], an excess of netrin-1 might promote cell survival in part through pathways independent of DCC and UNC5H. Second, in the genetically engineered mice there is a uniform gradient of netrin-1 in the intestinal lining, as well as overexpression of netrin-1 relative to its usual levels, which could lead to some doubts about the physiological relevance of the findings. However, Mazelin *et al.* did see increased cell death in intestinal crypts of mice deficient in netrin-1, implicating netrin-1 in the survival of normal intestinal cells.

Their findings are consistent with the notion that there might be strong selection for inhibition of DCC and UNC5H expression or function in colon and other cancers. The proteins might indeed function in tumour suppression, perhaps by inhibiting growth or causing the death of potential cancer cells in environments where the netrin-1 concentration is low. Conceivably, singular inactivation of *DCC* or *UNC5H* might be insufficient to promote tumour development. Concerted inactivation of both genes might be required for progressive outgrowth of cells in regions where netrin-1 levels are usually low, explaining why mice lacking one copy of the *Dcc* gene showed no overt predisposition to intestinal or other tumours[7].

To understand better the roles of DCC and UNC5H proteins as netrin-1 dependence receptors that regulate cell survival, it might prove useful to study other genetically engineered mice, such as mice with intestinal-specific deletions of the *Dcc* and/or *UNC5H* genes, or mice carrying *Dcc* or *UNC5H* mutations that are predicted to interfere with the receptors' ability to initiate cell death. Other dependence receptors have been identified[3] and yet others probably remain to be discovered, so further research should help to clarify whether alterations in dependence-receptor pathways have a more widespread role in cancer. ■

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