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Receptor sponge soaks up cancer cells

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A new study suggests that using 'dummy' receptors to bind to cell growth factors that are necessary for the growth and metastasis of pancreatic cancer could lead to the development of novel therapies for the disease. A similar concept is already in clinical use for rheumatoid arthritis. After introducing the gene for a soluble receptor of transforming growth factor-β (TGFβ) into usually aggressive human cancer cells, Murray Korc and colleagues (University of California College of Medicine, Irvine, CA, USA) found that mice with the cancer cells that produced the dummy receptor showed significantly reduced tumour growth and metastasis [1]. 'Binding TGFβ to a receptor that doesn't signal a cell to grow and spread can make that receptor literally 'sponge up' the excess TGFβ. If this is effective in humans, it may reduce the risk of spreading cancer cells, possibly increasing the chances of survival from pancreatic cancer,' says Korc.

Lack of therapies for pancreatic cancer

Pancreatic cancer is the fifth deadliest cancer in the USA and the seventh most deadly in Europe. Only 20% of the thousands of people that are diagnosed each year survive after one year, and five-year survival rates are less than 5% [2]. 'Pancreatic cancer is often diagnosed when it has already spread because in its early stages it does not cause symptoms. The lesions are difficult to visualize and the cancer cells have many gene alterations that enable them to grow and metastasize,' explains Korc. There are no curative non-surgical interventions and curative surgery is difficult to achieve because 90% of cases involve widespread and aggressive metastasis.

Growth factors linked to poor prognosis

Pancreatic cancer cells, like cancer cells from other sites in the body, frequently over-express TGFβ, of which there are three isoforms, β1, β2 and β3. The type of cancer at the centre of this study, pancreatic ductal adenocarcinoma (PDAC), exhibits overexpression of all three isoforms. Korc and colleagues had previously observed that a human pancreatic cancer cell line expressing sTβRII, a soluble form of the TGFβ receptor, showed attenuated tumour growth when injected under the skin of nude mice. 'It was not possible to find out if the expression of the soluble receptor also inhibited metastasis because subcutaneous tumours arising from pancreatic cells do not metastasize. In this study, we went further and tested the concept in a metastatic mouse model,' explains Korc.

Generating the growth factor 'sponge'

To do this, human PANC-1 cells were first transfected with a plasmid containing the soluble TGFβ receptor gene. Cells cultured from a positive clone were injected subcutaneously in nude mice and tumour size was measured until day 49, when the mice were killed. The subcutaneous tumours were then pooled and minced, and tumour fragments were introduced directly into the pancreas of other nude mice, which were then inspected for tumour formation by weekly palpation and, after two months, the mice were killed and examined for metastases. Mice implanted with PANC-1 cells carrying the sTβRII gene showed 72% less tumour growth than control mice implanted with the same cells but without the gene. Control mice developed large tumours (0.8–1.1 cm) and multiple metastatic lesions in the liver, spleen, local and distal lymph nodes. Of the eight experimental mice, only one developed a large primary tumour (1.2 cm) with peritoneal seeding and mesenteric lymph involvement. One mouse developed a medium-sized tumour (0.8 cm); three mice developed small tumours (0.3 cm) and three mice did not form any tumours; none of these seven mice showed any sign of metastasis [1].

A long way to go

James Abbruzzese (M.D. Anderson Cancer Center, University of Texas, Houston, TX, USA) thinks that the general concept of using soluble receptors to treat some types of cancer is an interesting one. 'Targeting cancers that overexpress TGFβ is valid because patients with this profile tend to have a much worse prognosis,' he says. However, he does warn that more research is required to understand the underlying mechanism at work and to investigate the therapeutic potential of this new strategy. 'Blocking the signalling pathway through which TGFβ stimulates growth of cancer cells may depend on the cell's pathway being intact. The PANC-1 cells used in this study have an intact Smad pathway [TGFβ acts through a series of protein messengers from the Smad family] but the effect of transfecting cells without an intact pathway has not been assessed,' he comments. TGFβ signalling is complex and when any of the Smad components are mutated (Smad is genetically absent in ~50% of patients with pancreatic cancer) and the pathway is dysfunctional, the effects of the sTβRII would be difficult to predict. In fact, because TGFβ can

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both stimulate and inhibit cancer cell growth [3] additional pancreatic cancer cell lines should be studied before any general approach to pancreatic cancer can be formulated. Abbruzzese points out that many pancreatic cancers also overexpress epidermal growth factor (EGF), which is usually stimulatory and which the Korc group has shown also leads to poor prognosis. 'We have recently reported a Phase II trial in which we used a monoclonal antibody directed against EGF in patients with EGF positive pancreatic cancer. When the C225 monoclonal was given with standard chemotherapy, patients did fare better than those given standard therapy alone [4]. Using a soluble EGF receptor may also achieve a similar result,' says Abbruzzese.

Currently, Korc and colleagues are testing other forms of the soluble receptor and the protein itself for potential therapeutic activity but Korc stresses that all of this work is preliminary. 'Ideally, we would like to move forward to clinical trials within three years but there is so much more to do before considering trying this approach in humans, it is difficult to set a more precise timescale,' he concludes.

References

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Computer chip that could restore sight

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An artificial retina could one day offer useful vision to people who suffer blindness caused by diseases such as retinitis pigmentosa or age-related macular degeneration (AMD). Researchers are developing computer chips that are designed to imitate basic photoreceptor cell function; the microchip is to be implanted on the retina, where it would substitute for damaged cells, stimulating healthy neurons in the visual pathway. Scientists at the University of Southern California (USC; Los Angeles, CA, USA) have now gained FDA approval to test their implantable computer chip system in clinical trials. They hope to bring a product on the market within 3–5 years.

Vision loss from retinal degeneration

The retina consists of several cell layers that line the back of the eye. The photoreceptor cells, which are classified as rods and cones, are responsible for converting light into electrical impulses. These are relayed to ganglion cells, which transfer the signal via the optic nerve to the brain. However, when the photoreceptor cells are damaged by diseases, such as retinitis pigmentosa or AMD, the retina cannot process the light and the brain never receives impulses to form a complete image.

Blindness caused by retinal degeneration is a big problem. In 1997, the World Health Organization estimated that approximately 8 million worldwide are blind or severely visually disabled because of AMD (http://www.who.int/inf-fs/en/fact144.html), a disease caused by the degeneration of photoreceptors in the macula, the central portion of the retina responsible for perceiving fine visual detail. AMD is the most common cause of vision loss in older people and, because the global population is ageing, numbers are expected to increase further.

The number of people affected by retinitis pigmentosa is much smaller, but symptoms, such as loss of peripheral vision or night blindness, are already recognized in adolescents and young adults. The name retinitis pigmentosa refers to a group of inherited diseases that cause the degeneration of photoreceptors; the condition deteriorates throughout life.

Current treatment options for people with retinal degeneration are poor. Peter Dudley at the National Eye Institute (Bethesda, MD, USA) says, 'There is a real need to fix the problem.' The most popular approach to finding a cure is to look for a genetic culprit. 'But that has been difficult,' says Dudley, 'simply because it is like many complex diseases, such as diabetes, where you are likely to have many factors involved in the disease.'

An artificial retina

In an alternative approach, groups in the USA, Germany and Japan are working on strategies to bypass the damaged retina with an implantable computer chip. One

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