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planned for late 2006. Benitec (Sydney, Australia) also plans to enter Phase I trials with an RNAi-based HIV antiviral in 1H 2006 and a hepatitis C treatment in 2H 2006. In the longer term it is hoped that RNAi could be used to attack cancer cells, and several compounds are in preclinical development.

References

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Resisting resistance

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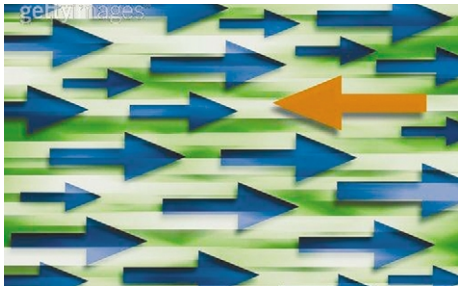
Cancer patients undergoing long-term chemotherapy increasingly endure their tumours developing resistance to the drugs they need. New research by a group led by Bryan Toole, Professor in the Department of Cell Biology and Anatomy, Medical University of South Carolina, USA, have discovered a method of inhibiting a series of reactions leading to the development of drug resistance.

Surprise role for hyaluronan

Resistance to chemotherapeutic drugs normally develops as a result of upregulation of transport proteins that remove the drugs from the cancer cells. The team at South Carolina has elucidated some of the pathways that make this possible – and potentially identified a way to prevent resistance developing.



Toole's group previously showed that small pieces of a polysaccharide – hyaluronan – were able to sensitize previously drug-resistant cancer tissue to a number of chemotherapeutic agents. Hyaluronan is a large polysaccharide that is normally found as part of the structure of the extracellular matrix. As hyaluronan is largely structural in function, it came as a surprise to learn that it has recently been identified as crucial to signalling pathways in the development of tumours. Furthermore, hyaluronan has been shown to stimulate drug resistance in cancers. It's also been seen that, via a complex signalling pathway, hyaluronan stimulates its own production. Elements of this signalling loop – including hyaluronan itself – stimulate expression the multi-drug transporters that cause drug resistance. 'Effectively, the response to hyaluronan is responsible for drug resistance,' said Toole.

> 'The oligosaccharides are fairly readily made'

Clear but unproven potential

There's a twist to the tale, however. Toole's group have also been able to inhibit hyaluronan from entering this ever-amplified resistance loop. By taking oligomers of hyaluronan – effectively small pieces of the polysaccharide – the team were able to stop hyaluronan from binding to its natural receptor, CD44, stopping the signalling that leads to resistance. 'The oligomers bind to the same receptor,' Toole added. 'They bind, but don't induce the same reaction.' By displacing the polymer from its receptor, the team have discovered a way to block drug resistance.

Not only do the oligomers block the development of resistance, they have also been shown to sensitize resistant cancer cells to chemotherapeutic drugs, even reverse the malignant properties of cancers. 'This work is very interesting,' agreed Timothy Hardingham, Professor of Biochemistry at Manchester University, UK. 'And somewhat out of the blue and unpredicted from the known properties and activities of hyaluronan.'

'There is potential for the development of small molecule antagonists at the CD44 receptor,' said Toole, 'but possibilities already exist with peptides.' He continued, 'Peptide hyaluronan mimetics have been around for little while now and can antagonize hyaluronan, but they've not been tested in biological systems yet.' Hardingham agrees; 'There is a clear potential, but as yet unproven scope for translating this to therapy.'

Readily available

Conventional drug development approaches might not be necessary, as the oligosaccharides are not only effective but also, it seems, readily available. 'The oligosaccharides are fairly readily made', Toole added. 'There's already a hyaluronic acid industry out there, serving the cosmetic industry and for eye and knee surgery. The degradation product would be just as readily available.' The degradation products would serve as a steady supply of hyaluronic oligosaccharide antagonists. 'Hyaluronan can also be made by bacteria – another potential source,' added Toole.

The future for this research, then, might soon be of benefit to patients. Toole continued, 'Using hyaluronan antagonists in combination with regular chemotherapy will allow reduction of chemotherapy dosage, meaning less toxic side effects.'

Reference

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Cell cycle inhibitors key to neoangiogenesis

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Cancerous tumors insidiously co-opt building blocks for neoangiogenesis – the construction of blood vessels to nourish a growing mass of cells. An emerging picture of the process shows that cell cycle inhibitors are crucial, and the most recent work now singles out p27 and p130 as key molecules. A collaborative team headed by Andrew Koff at Memorial Sloan-Kettering Cancer Center and David Lyden at Weill Medical College of Cornell University

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targeted the inhibitors in hopes of hampering vessel development [1].

An adult problem

Unlike most stem cell research, neoangiogenesis is a problem of adult, not embryonic, stem cell differentiation – which involves a different environment and set of regulatory molecules. There is still debate as to whether new blood vessels arise from the cells of existing networks, or they must be crafted from progenitor cells. In the current study, the researchers focused their attention on the latter – specifically on hematopoietic and endothelial progenitor cells.

They created transgenic mice that were deficient for the p27 and p130 cell cycle inhibitors. These double-knockout mice expressed pituitary tumors, says Lyden, in which 'the whole blood supply was almost absent, it was necrotic.' They distinguished between the effects on hematopoietic and endothelial progenitor cells by transplanting bone marrow tissue from the double-knockouts to healthy animals.

Both cells are derived from bone marrow and are important to blood vessel formation. Neither circulates in a healthy adult; their presence indicates major injury or cancer. Vascular endothelial growth factor (VEGF), a cytokine normally absent, is produced in earnest by a tumor. VEGF then circulates in the blood stream and recruits stem cells that express VEGF receptors, coaxing them out of the bone marrow.

Cells on the move

Once VEGF binds receptors expressed by progenitor cells, they undergo proliferation and expansion, during which they migrate from a bony compartment to blood vessels within the bone marrow. Next comes mobilization, in which the cells make the leap to the blood stream and are targeted to the tumor source. Finally, the cells differentiate and are incorporated to new blood vessels. The cell cycle inhibitors appeared to act on the progenitor cells during this journey – and, says Lyden, 'all the steps seem to be affected in some way.'

'the whole blood supply was almost absent, it was necrotic.'

A point of uncertainty was whether hematopoietic and endothelial stem cells originated from a single or several cell types, and whether these cells occupied the same space. Lyden says their results showed 'that the stem cell populations are distinct in bone marrow, and they come from different niches.' This understanding of "where they are, where they originate", gives us more information about how to target them.' And targeting them more directly is a major aim. Lyden suggests a scenario in which an antibody to the VEGF receptor would be combined with molecules targeting the p27 and p130 cell cycle regulators. With that combination, he says, you could prevent cells from exiting to the blood stream, getting to the tumor, and ultimately from forming new blood vessels.

Transcriptional regulation in tumour development

Just exactly how the two factors promote angiogenesis is not clear, says Koff, but they do know that it involves cyclin E kinase, a signal critical to transcription during differentiation. They believe that 'either the cell cycle inhibitors mop up the kinase, which could stop transcription, or that the factors interact directly with the transcriptional apparatus.' The combined loss of p27 and p130 left cells with high levels of cyclin E kinase, which might have been sufficient to block exit from the cell cycle.

Robert Weinberg of the Whitehead Institute also works on the puzzle of cancer neoangiogenesis. He called the work 'quite interesting,' but expressed scepticism that the cell cycle inhibitors might themselves provide anti-cancer therapeutic targets. Nevertheless, Lyden and Koff are hopeful that new connections between the cell cycle and angiogenesis will yield a clearer understanding of tumor development.

Reference

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