'very little toxicity,' says Benedict. 'The Ad-interferon [appears to be] a different drug than interferon protein. It is interferon but it's more than interferon.' Although this could lead to a treatment for superficial bladder and other cancers, 'all this is qualified,' says O'Donnell. 'We can do really well curing mice of their cancer. It seems to be a lot more complicated with people.'

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The fight against cancer: the next round

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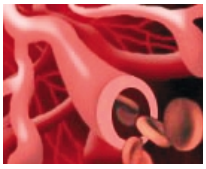

It has now been almost three decades since it was first proposed that inhibition of angiogenesis (the formation of new blood vessels) could play a crucial role in the treatment of cancer. However, it has taken quite some time for 'anti-angiogenesis' drugs to become a reality within the clinical setting, and despite early enthusiasm, they have failed to make a dramatic impact in clinical trials. In Phase III trials that have been conducted to date, these drugs have not resulted in significant increases in survival rates, and toxicity within the patient remains an issue. Scientists at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins (http://www.hopkinskimmelcancercenter.org/) have shown that combining two different types of drugs in a 'one-two punch' type of therapy might be more effective in the treatment of cancer than single agents [1].

The armamentarium

Angiogenesis plays a pivotal role in tumor growth, invasion and metastasis. Normal endothelial cells are usually quiescent, dividing approximately every seven years. However, in malignant cells accelerated growth occurs, with cells sometimes dividing as often as once per week. Up until this point of accelerated growth commences, it is usually genetic and epigenetic alterations that are responsible for deregulated tumor growth.

However, beyond a certain size tumors require certain nutrients and oxygen to grow; signaling between various growth factors and endothelial receptors is responsible for endothelial cell survival, proliferation, differentiation and angiogenesis, which are necessary to allow this growth to take place. As a result, many researchers have focused on vascular endothelial growth factors (VEGF) and corresponding receptors as targets for anti-angiogenesis therapy.

The interaction that takes place between VEGF and its receptors activates receptor-associated kinase activity and crucial signaling pathways that lead to tumor angiogenesis. One such drug that has been clinically developed is designated PTK787/ZK222584; this agent selectively and potently inhibits the VEGF receptor tyrosine kinase and has previously been shown to inhibit VEGF-mediated angiogenesis in phase I studies [2].

The one-two punch

Roberto Pili and his colleagues at the Johns Hopkins Kimmel Cancer Center applied a combination approach to target tumor growth and angiogenesis by using both PTK787/ZK222584 and a histone deacetylase (HDAC) inhibitor, designated NVP-LAQ824, in mouse and cell-line models [1]. 'Combining these two types of drugs may have a greater impact on cancer development than using them alone,' says Roberto Pili. 'Our idea is to attack the way cancers form new blood vessels by disrupting the angiogenesis process in two different cells.'

HDAC inhibitors represent a class of therapeutic agents that act against tumors through chromatin remodeling and modulation of gene expression, thereby affecting the cell cycle and survival pathways. During tumor development, acetyl groups are removed from histones, forcing the DNA to remain tightly coiled and restricting gene activation. HDAC

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inhibitors reverse this error by blocking the enzymes that remove the acetyl groups; as a result, DNA can unwrap itself and make the required gene products. In their study, Qian *et al.* [1] reported that treatment with the HDAC inhibitor NVP-LAQ824 alone affected tumor and endothelial cells and was associated with increased histone acetylation, p21 upregulation and growth inhibition. Treatment with this agent also inhibited the expression of a number of angiogenesis-related genes, such as *angiopoietin-2*, *Tie-2* and *survivin*, in endothelial cells, and downregulated hypoxia-inducible factor 1-α and VEGF expression in tumor cells.

When the HDAC inhibitor was combined with the angiogenesis inhibitor PTK878/ZK222584, the number of endothelial cells in culture dishes was reduced by 51%, compared with only 21% reduction when used individually. 'VEGF inhibitors are know to have most effect on endothelial cells, the bricks and mortar of blood vessels,' explains Pili. 'However, HDAC inhibitors target both endothelial and epithelial cells, which line organs, and are the origin of many cancers.'

When these drugs were applied in combination to mice that had prostate and breast cancer, prostate tumor development was reduced by 85%; this was compared with 35% and 75% when the mice were treated with VEGF and HDAC inhibitors, respectively. The combination treatment was also more effective against breast tumor development, with an ~80% inhibition in tumor growth being observed; this was compared with 54% and 60% tumor growth reduction when the inhibitors were used on their own. Importantly these effects were obtained without the adverse side effect of toxicity.

The results reported in this study [1] suggest that such combination therapy might represent a novel therapeutic approach to the fight against cancer and are so promising that preliminary testing of similar drug combinations in humans is now planned.

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Ontology-based knowledge management of troglitazone-induced hepatotoxicity

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Drug safety and development has serious limitations in the use of all available knowledge for efficiency and risk prediction because the underlying knowledge is complex and diverse. Here, a system that enables the prediction and discovery of meaningful associations of possible adverse drug reactions (ADRs) with drug treatments by *in silico* pre-screening is introduced. The presented ontology-based knowledge management method enables efficient analysis and visualization of complex knowledge and data, which are not penetrable without auxiliary means. Such analysis enables the early identification of patients with a potentially elevated risk for the development of serious ADRs when exposed to an offending drug. Moreover, the evaluation enables the recognition of crucial substructures in drugs, which could be defused or deactivated in an appropriate secondary drug design. The example discussed here is troglitazone-induced hepatotoxicity, which is displayed variously by patients with different genotypes.

Drug response variability

The person-to-person variability of drug response is a major problem in drug development and clinical practice [1]. It can lead to both ADRs or therapeutic failure in individual patients or in sub-populations of patients. A meta-analysis of ~40 prospective studies in hospitals in the USA indicates that 6–7% of inpatients might suffer from serious ADRs and 0.32% of patients have fatal ADRs [2]. Overall, this results in ~100,000 deaths per year caused by serious ADRs, making them the fourth

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