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Targeting tumors by necrosis

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A study led by Craig Thompson at the University of Pennsylvania, USA (http://www.upenn.edu) advances our understanding as to how and why some cancer cells die and others do not in response to existing chemotherapy [1].

The poor relation

This is the first study to show that cancer cells can be selectively targeted by drugs that induce necrotic cell death. Necrosis was considered to be an unregulated process and has long been the 'poor relation' in studies of cell death in animals, with scientists focusing their attention on apoptosis, a more ordered regulated cell death-pathway.

'Necrosis has lacked a molecular definition in contrast to apoptosis where specific genes have been identified that regulate the process of cell death. The identification of apoptotic regulators has led to targeted therapeutics to modulate the death process in disease', said Eileen White from Rutgers University, USA (http://www.rutgers.edu/). 'Genetic modulators of necrosis (or indeed the altered metabolism displayed by many tumors) may be similarly useful for therapeutic intervention', she added.

Aerobic glycolysis

To understand how cells that are resistant to apoptosis die in response to DNA-alkylating agents, Craig Thompson and his team examined mouse fibroblasts that were deficient in p53, Bax and Bak – proteins necessary for apoptosis. They found that the cell actively initiates its own death in response to these drugs. Following DNA damage the cells activate PARP – an

enzyme that can increase the accessibility of DNA to DNA-repair enzymes. Necrosis as a result of DNA alkylating agents requires PARP, although it's not sufficient to sensitize the cells. 'Our results suggest that agents that induce necrosis through activating PARP will be effective only against tumors that depend on glycolysis', said Thompson. Aerobic glycolysis is a characteristic of cancer cells making these agents highly specific.

'At the moment there are no examples of chemotherapeutic drugs that activate PARP directly. All the ones so far activate PARP indirectly by damaging DNA', said Thompson. His group is interested in the development of these drugs because they have advantages over those currently in use. 'We believe they would be safer chemotherapeutic agents since they wouldn't damage DNA and increase the risk of secondary malignancies in patients', he added.

Programmed necrotic death

Commenting on the disadvantages of the necrosis-inducing drugs, Thompson said, 'The current ones are associated with the risk of damaging DNA and causing additional mutations but I believe safer more effective ones can be developed now that we have defined the regulatory components of programmed necrotic death'. Echoing his concerns, White added 'A possible disadvantage to killing tumor cells by necrosis could be the induction of an inflammatory response which may create a damaging tumor microenvironment'.

However, exploiting cell death to control cancer might require a combination of approaches. 'As combinatorial drug approaches are likely to be required for successful responses, the more distinct pathways we can identify and target, the better', said White. 'I believe combinations of drugs that induce selective necrosis of cancer cells would be better than combinations that target apoptosis', added Thompson.

Many obstacles remain in the path of effective tumor-specific therapy or personalized medicine. However this study has brought us one step closer. 'Cancer is a complex disease and we need to link the genetic defects of specific tumor types with effective therapeutics. Linking altered tumor metabolism with the responsiveness to alkylating agents may explain their mode of action (or inaction as the case may be)' said White. Meanwhile, Thompson's group is testing the significance of their results in animal tumor studies.

Reference

1 Zong, W-X. *et al.* (2004) Alkylating DNA damage stimulates a regulated form of necrotic cell death. *Genes Dev.* 18, 1272–1282

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