patients with active MM, circulating proteasome level was a significant prognostic factor, as were the established indicators β2-microglobulin, C-reactive protein, chromosomal deletion 13q14 and high-dose chemotherapy. Circulating proteasome level proved to be the most powerful independent prognostic factor on the basis of a multivariate analysis.

This study has convincingly shown that the circulating proteasome level is correlated with advanced disease in patients with MM, is sensitive to disease activity and is useful in predicting survival. Further studies are warranted to establish the value of this marker in monitoring patients treated with the new class of drugs that directly inhibit the ubiquitin–proteasome system.

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**ORIGINAL RESEARCH PAPER** Jakob, C. *et al.* Circulating proteasome levels are an independent prognostic factor for survival in multiple myeloma. *Blood* 9 November 2006 (doi 10.1182/blood-2006-04-016360)

breaks were seen. Western blot analyses indicate that the *Mcm4*$^{Chaos3}$ mutation destabilizes the MCM4 protein, and levels of MCM7 were also reduced.

Analysis of the *Mcm4*$^{Chaos3}$ mutation in an inbred mouse strain indicates that this allele is oncogenic in females. Most homozygous *Mcm4*$^{Chaos3}$ virgin mice developed breast adenocarcinomas by 12 months of age.

It has been proposed that a reduced number of licensed DNA replication origins might compromise the fidelity of DNA replication (and therefore chromosomal stability), especially in conditions of replication stress. These findings add weight to this argument and show that the MCM proteins could function as tumour suppressors. Further investigations are required to address why *Mcm4*$^{Chaos3}$ mice are prone to mammary tumours.

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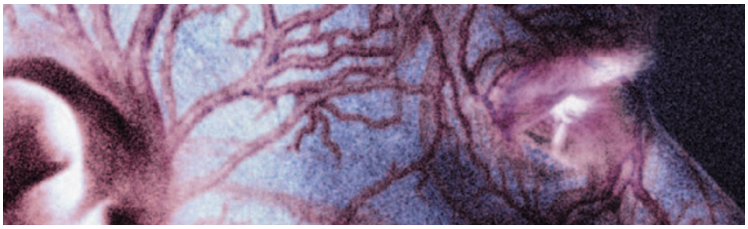
**ORIGINAL RESEARCH PAPERS** Shima, N. *et al.* A viable allele of Mcm4 causes chromosomal instablility and mammary adenocarcinomas in mice. *Nature Genet.* AOP 3 December 2006 (doi: 10.1038/ng1936)



**TUMOUR MICROENVIRONMENT**

# Remodelling resistance

Patients with glioblastoma invariably fail to achieve long-term survival, which is thought to result from acquired resistance to chemotherapeutics or radiation, and is associated with the expression of transglutaminase 2 (TG2). Keith Rich, David Piwnica-Worms and colleagues show that small-molecule inhibitors of TG2 can overcome resistance to chemotherapy.

TG2 has many functions, including stabilizing fibronectin in the extracellular matrix (ECM). This is thought to enable the interaction of fibronectin with cellular integrins, setting up an anti-apoptotic cell–ECM signalling network that promotes glioblastoma cell survival. Indeed, the inhibition of TG2 in combination with the chemotherapeutic alkylating agent *N*,*N*′-bis(2-chloroethyl)-*N*-nitrosourea (BCNU) in a mouse glioblastoma xenograft model has previously been shown to increase apoptosis and reduce tumour weight. However, how the inhibition of TG2 activity sensitizes glioblastoma cells to chemotherapy remains unclear.

Using frozen anaplastic astrocytoma and glioblastoma samples, the authors show that TG2 activity and expression is significantly increased compared with normal brain tissue. The increased expression of TG2 in the ECM correlated with an abnormally dense linear assembly of fibronectin. Moreover, using fresh glioblastoma tissue they showed that TG2 and fibronectin are also overexpressed and abnormally organized in regions of the brain that have infiltrating tumour cells. So, is the abnormal expression of fibronectin functionally significant and caused by the increased expression of TG2? The authors show that the TG2 small-molecule inhibitor KCC009 prevents the assembly of fibronectin into dense strands along the cell surface of U87MG glioblastoma cells. Furthermore, mice with orthotopic glioblastoma (derived from injected DBT-bioluminescent glioblastoma cells) that were treated with KCC009 had reduced abnormal fibronectin expression that correlated with reduced TG2 activity. The relationship between fibronectin assembly and TG2 activity was also confirmed by RNA interference of *TG2* in U87MG cells.

Finally, the authors investigated whether KCC009 could sensitize DBT orthotopic tumours to BCNU. Using bioluminescence imaging, they showed that only KCC009 in combination with BCNU resulted in a significant reduction in tumour size. The tumours were analysed for levels of apoptosis, and mice treated with KCC009 and BCNU combination therapy had increased levels of apoptosis compared with mice treated with each drug seperately. Similarly, monotherapy failed to increase the survival of the mice, unlike treatement with KCC009 and BCNU.

Remodelling the ECM is thought to provide a permissive environment for tumour growth. The authors suggest that KCC009 prevents the TG2-dependent remodelling of fibronectin, thought to function in pro-survival signalling in glioblastomas. Therefore, targeting factors that promote permissive remodelling of the ECM, such as TG2, could be a new approach to sensitizing glioblastoma cells to chemotherapy.

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**ORIGINAL RESEARCH PAPER** Yuan, L. *et al.* Transglutaminase 2 inhibitor, KCC009, disrupts fibronectin assembly in the extracellular matrix and sensitizes orthotopic glioblastomas to chemotherapy. *Oncogene* 13 November 2006 (doi:10.1038/sj.onc.1210048)