IN BRIEF

CHEMOTHERAPEUTICS

A bacterial protein enhances the release and efficacy of liposomal cancer drugs.

Cheong, I. *et al. Science* **314**, 1308–1311 (2006)

Bert Vogelstein and colleagues show that *Clostridium novyi-NT*, an attenuated anaerobic bacterium, selectively infects hypoxic tumour microenvironments. Once established in the tumour, the bacteria can increase the release of liposome-encapsulated chemotherapy drugs such as doxorubicin or irinotecan. Using a combination of the attenuated bacteria and liposomal doxorubicin or liposomal irinotecan resulted in complete tumour regression and increased the survival of mice with large, established human colorectal cancer xenografts or colon CT26 mouse tumours. Furthermore, *Clostridium novyi-NT* increased sixfold the concentration of drug that the tumour cells were exposed to. However, treatment with monotherapies or non-liposomal drugs in combination with *Clostridium novyi-NT* did not increase survival or prolong tumour regression. The secretion of liposomase, the *Clostridium novyi-NT*-specific lipase, was shown to be the probable cause of the liposome-disrupting ability of the bacteria. Unlike other bacterial lipases, liposomase can alter lipid bilayer structures and disrupt liposomes *in vitro*. Therefore, the development of *Clostridium novyi-NT* or liposomase as adjuvant therapies combined with liposomal chemotherapy drugs could substantially improve the specific targeting of tumour cells.

DIFFERENTIATION

GATA-3 maintains the differentiation of the luminal cell fate in the mammary gland.

Kouros-Mehr, H. *et al. Cell* **127**, 1041–1055 (2006)

During puberty, the mammary gland differentiates from multipotent progenitor cells into myoepithelial cells or luminal epithelial cells, the cell type from which breast cancer develops. Zena Werb and colleagues now show that the transcription factor GATA3 is essential to this process. Using an RNA-based genome-wide microarray screen they show that Gata3 is the most highly expressed transcription factor in mouse differentiating and mature mammary epithelium. Furthermore, a conditional Gata3 knockout mouse was used to show that the transcription factor is essential for the pubertal development and maintenance of the mammary gland. Gata3 loss in adult mice resulted in the proliferation of undifferentiated cells and the detachment of existing epithelial cells from the basement membrane. Reduced expression of GATA3 in breast cancers is associated with a poor prognosis. This work suggests that GATA3 loss might have a causal role in breast cancer progression and metastasis.

PREVENTION

Prevention of Brca1-mediated mammary tumorigenesis in mice by a progesterone antagonist.

Poole, A. J. *et al. Science* **314**, 1467–1470 (2006)

How does BRCA1 suppress tumorigenesis in hormone-sensitive tissues? Eva Lee and colleagues show that Brca1/Trp53-deficient mice have a defect in the progesterone receptor (PR)-degradation pathway that results in PR overexpression in mammary epithelial cells. Mammary tumorigenesis was prevented in the Brca1/Trp53-deficient mice by treatment with mifepristone, a progesterone antagonist. Therefore, antiprogesterone treatment might to prevent breast cancer in individuals with BRCA1 mutations.

PROGNOSIS

Prognostic proteasome

Proteasome levels in the blood are increased in patients with malignancies that are known to overexpress components of the ubiquitin–proteasome system. A longitudinal study has now shown that measuring the levels of circulating proteasomes in patients with multiple myeloma (MM) has prognostic value.

Orhan Sezer and colleagues used an enzyme-linked immunosorbent assay (ELISA) based on the 20S catalytic core complex of the proteasome to measure proteasome levels in sera from 141 previously untreated patients with MM. Serum samples were also drawn from 50 healthy individuals and from 20 patients with monoclonal gammopathies of undetermined significance. Compared with both these control groups, patients with MM had significantly increased levels of circulating proteasomes. In addition, patients with active MM had significantly higher levels than those with smouldering disease.

The authors examined the effect of treatment on circulating proteasome levels in patients with active MM who received first-line chemotherapy. Levels declined significantly in patients who achieved a complete or partial remission after treatment, whereas non-responders showed no change. Importantly, treated patients whose circulating proteasome level returned to normal had significantly prolonged survival relative to responders with a high post-treatment level.

The authors also evaluated the potential of the serum proteasome level to predict patient survival. In univariate analyses of samples from

TUMORIGENESIS

Licensed to cause chaos

Mini chromosome maintenance (MCM) proteins 2–7 are part of the machinery that licenses DNA replication. Naoko Shima and colleagues now show that a single amino-acid change in MCM4 induces breast adenocarcinomas in mice.

Using a chemical mutagenesis screen in mice to identify genes that affect chromosomal stability, the authors had previously found a mutation — *Chaos3* — that results in increased levels of micronuclei in red blood cells, an indicator of chromosome instability; the young mice were otherwise normal. *Chaos3* was mapped to a region that includes *Mcm4*, and sequencing showed a T–A transversion in *Mcm4* that results in a single amino-acid change in a residue that is highly conserved and potentially important for MCM protein interaction.

To investigate further, the authors made a mouse line that carries a mutant *Mcm4* allele (*Mcm4*$^{-}$), in which the highly conserved MCM domain is disrupted. *Mcm4*$^{-}$ heterozygotes are normal, with a normal level of micronuclei in red blood cells, but the homozygotes are inviable. A series of matings between *Mcm4*$^{-}$ and *Chaos3* mice indicated that *Mcm4*$^{-}$ is probably a null allele owing to the more extensive mutation of the protein, whereas *Mcm4*^{Chaos3} is a hypomorphic (reduced activity) allele that might have a dominant function in terms of chromosomal instability.

Further experiments in *Mcm4*$^{-}$; *Mcm4*^{Chaos3} and *Mcm4*^{Chaos3};*Mcm4*^{Chaos3} mouse embryonic fibroblasts indicated that in standard culture conditions there was no evidence of chromosomal instability. However, if the cells were treated with aphidicolin to induce DNA replication stress, increased levels of chromosomal