Molecular Cancer Research Highlights

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Selected Articles from This Issue

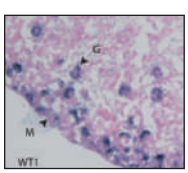
## Tumor TIMP-2 Induces Endothelial Barrier Dysfunction

Shen et al. Page 939

Matrix metalloproteinases (MMP) have been implicated in multiple stages of cancer metastasis. The molecular basis underlying their regulation and associated cellular responses during metastatic extravasation has not been established. In this study, Shen and colleagues present evidence that breast cancer cell adhesion to lung microvascular endothelial cells induces MMP-2 activation, which increases endothelial permeability and tumor cell transmigration. They have further identified cancer cell--derived TIMP-2 as a major determinant of endothelial MMP-2 activity in the presence of MMP-14. Their findings suggest a cooperative mechanism between metastatic tumor cells and endothelial cells in regulating MMP-2 activation and tumor cell transmigration.

## Scribble Is a Target of WT1(+KTS)

Wells *et al.* Page 975

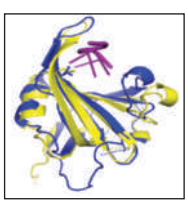



*WT1* encodes a tumor suppressor that is necessary for the proper development of multiple organs and is frequently inactivated in a subset of cancers. To understand the function of the most prevalent WT1 isoform, whose DNA binding domain is disrupted by a three-amino acid (KTS) insertion, Wells and colleagues undertook a genome-wide chromatin immunoprecipitation and cloning analysis to identify candidate transcriptional target genes. Their results suggest that this *WT1* isoform encodes a DNA-binding transcriptional regulator that functionally links the key planar cell polarity gene *SCRIBBLE* to regulation of renal development and tumorigenesis.

## Function of RPA1-L221P

Hass *et al.* Page 1017

Replication Protein A (RPA) is essential for cellular DNA metabolism. Mutation of a conserved leucine residue in the DNA-binding site of RPA causes genomic instability and a high cancer rate in heterozygous mice. Hass and coworkers have used functional assays in cells and in vitro to determine the molecular defect of the homologous human RPA mutation. This mutation produces a stable nonfunctional complex. These results suggest having one functional and one nonfunctional RPA allele is not sufficient to maintain long-term genomic integrity. This study provides insights into the genetic causes of cancer.



## 5-AzaCdr Induces Stable Demethylation at TMS1

Kagey *et al.* Page 1048

Aberrant promoter DNA methylation silences critical regulatory genes in human cancers and is potentially reversible through treatment with DNA demethylating agents. Although these agents induce clinical responses in leukemias, their effects are relatively transient, thus requiring extensive maintenance therapy. To understand the molecular mechanisms that control DNA remethylation, Kagey and colleagues characterized epigenetic alterations that accompany DNA demethylation and subsequent remethylation. Distinct locus-specific differences in the kinetics of DNA remethylation were observed and correlated with the ability to attain and subsequently maintain RNA polymerase II occupancy. A better understanding of the epigenetic events leading to resilencing of tumor suppressor genes may help to identify additional targets for therapeutic intervention.

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# Highlights of This Issue

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