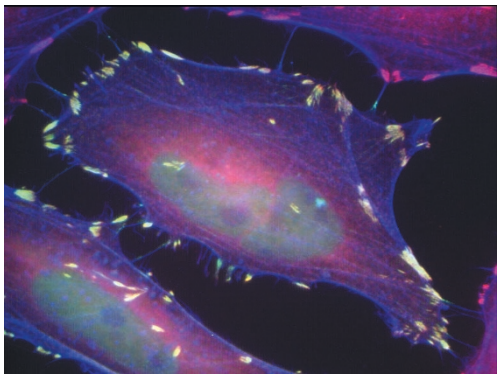
TES of the focal adhesions

focus on *cell polarity*

How to link the outside world to the intracellular environment is a complex, yet important, problem for any cell. Integrin focal adhesion complexes are fundamental in maintaining this link, ensuring the extracellular matrix is firmly connected to the actin cytoskeleton. Over the last 15 years, numerous components of the focal adhesions have been identified. Now, two papers by Amanda Coutts and colleagues (*J. Cell Sci.* **116,** 897–906 (2003)) and Boyan Garvalov and colleagues (*J. Cell Biol.* DOI: 10.1038/jcb20021101S (in the press)) have recognised that a proposed tumour suppressor, TES, is also found within this array of signalling and adhesion molecules.

TES is a widely expressed protein that could have a role in regulating the growth of human cancer cell lines. Through sequence analysis, it was apparent that the protein contained three LIM domains, suggesting that TES is involved in regulating the cytoskeleton. Both groups set out to investigate the function of this protein, and in particular the LIM domains, further. Through localization studies it became clear that TES was indeed found in focal adhesions, as well as along actin stress fibres. In addition, Coutts and colleagues also propose that TES is localized to sites of cell–cell contact. Whereas localization to focal adhesions seemed to require the LIM domains, Coutts and colleagues showed that a 'LIM-less' version of TES is only found on actin stress fibres. Garvalov and colleagues also found that a LIM-less version localizes to actin stress fibres; however they found that some LIM was still localized to focal adhesions. This clearly indicates that different regions of TES are involved in regulating its localization to different cellular compartments.

In a yeast two-hybrid screen, Coutts and colleagues identified many proteins that could bind to TES, including Mena, a regulator of the actin cytoskeleton, and Zyxin, a component of the focal adhesion. Through pull-down assays, Garvalov and coworkers independently confirmed these results in HeLa cells and determined that the interaction with Zyxin is direct and demonstrated an interaction with VASP, another actin regulator. Using an inhibitory RNA approach, Garvalov and colleagues propose that Zyxin regulates the localization of TES to the focal adhesions, whereas Coutts and colleagues suggest that cells overexpressing TES have an increased ability to spread on fibronectin. Interestingly, it seems that TES can also bind to itself. This could allow the molecule to not only regulate its conformation, and hence its interaction partners, but also its localization and function.



Localization of C-term-TES to focal adhesions in HeLa cells. The actin cytoskeleton is shown in blue, the focal adhesion component paxillin is shown in red and green fluorescent protein (GFP)–C-term-TES is shown in green. Image provided by B. Garvalov and M. Way.

The functional analysis of other tumour suppressor genes has shown that many are involved in regulating cell–cell adhesion, migration and polarity, and in that respect TES would not seem to be unusual. What is different is the ability of TES to form intramolecular interactions that affect the binding status of the protein to focal adhesions and the actin cytoskeleton. A tumour suppressor gene that can regulate the molecules to which it binds, and hence the cellular function it can have, is a dangerous protein indeed.

SARAH GREAVES

incorporated in the nucleosomes of anti-silenced genes. To rigorously exclude the possibility that Htz1 functions by binding to boundary elements, Meneghini and colleagues looked for synergistic interactions between *htz1Δ* and a deletion of the well-characterized boundary element (be) that flanks the HMR locus. They observed a significant increase in Sir3 spreading in the *htz1Δ beΔ* double-mutant when compared with either single mutant, which is only consistent with Htz1 acting independently of the boundary element. Thus, incorporation of Htz1 in nucleosomes seems to be a second, novel mechanism to protect euchromatin from the inappropriate spreading of heterochromatin.

What are the structural features of H2A.Z that alter nucleosome functions to promote its anti-silencing activity? H2A.Z, an essential histone variant found in all higher eukaryotes, is highly conserved, with ~90% sequence identity among different organisms. However, it shares only ~60% sequence identity with major H2A, suggesting a unique function. Other histone variants have already been linked to specific roles. For example phosphorylation of H2AX is linked to DNA double-strand breaks, whereas macroH2A is enriched in the inactivated X chromosome[7,8]. Similarly, variants of histone H3 seem to function in centromere function (Cid)[9] and may also be involved in gene regulation (H3.3)[10]. Biochemical studies have shown that nucleosome arrays containing H2A.Z are more resistant to condensation, and thus the mere presence of H2A.Z-containing nucleosomes might interfere with condensation features required for heterochromatin. In addition, the interaction between the H3–H4 tetramer and the H2A.Z–H2B dimer is weakened by the presence of H2A.Z, thus lowering the energy of activation for polymerase migration through such chromatin structures. Recent studies have indicated that H2A.Z–H2B dimers are more readily released during transcription by Pol II, leaving behind a hexameric nucleosome structure on the DNA that seems to be positioned at the same location as the initial octamer[11]. Interestingly, this might also be a way to exchange H2A–H2B dimers with H2A.Z–H2B dimers and thereby allow the DNA to become locked into an active chromatin state.

This study introduces a novel mechanism to restrict silencing and simultaneously raises a host of new unresolved questions. The most pressing of these will be whether H2A.Z is in fact the signal that protects euchromatin, or whether H2A.Z deposition at anti-silenced regions is merely the consequence of an