confirm this prediction, along with the existence of faster relaxation processes originating from material near the ends of chains. Proximity to a chain end means a more rapid release from entanglements.

The flow and relaxation of entangled macromolecular fluids are extremely sensitive to molecular structure, as well as simply molecular weight. The inclusion of just one trifunctional branch point per polymer molecule (thus fashioning "star polymers") changes the entire shape of the spectrum of mechanical relaxation times. More complex architectures give whole families of different fluids, all exploring the same local field of entanglements but with different global consequences. Careful chemical synthesis of controlled molecular structures has gone hand-in-hand with physical experiment and theory (*3*).

But what if the molecular structures are not fixed on exit from the reaction vessel but are free to adapt to their surroundings? Such "living systems" abound with processes such as chain-scission, end recombination, branching, and end exchange, all of which may occur on time scales that affect the entanglement structure. The example most feverishly studied is the case of wormlike surfactant micelles. When aggregating surfactant molecules would rather form cylinders than spherical assemblies, the rodlike structures so formed may grow to huge lengths, at which they become flexible and entangle with each other, just like ordinary polymers (this is the mechanism behind the viscoelasticity of some shampoos). There is one important difference: the "polymers" undergo a perpetual partner-chase, breaking and recombining whole sections at rates that may greatly exceed the reptation time of the average chain. Theory and experiment (*4*) confirm that in this case, a remarkable "motional narrowing" occurs, and the viscoelasticity displays a single relaxation mode.

If the surfactants show us that self-assembly in polymer liquids can lead to simpler fluid behavior, then a more recent case illustrates that it can also increase its complexity and richness. A group of us at Leeds recently reported self-assembled polymers with a local tapelike structure based on highly anisotropic β sheets of model peptides (*5*). The rheological evidence points to a "reptation reaction" regime of behavior along the chain contours like the wormlike micelles, but at least one other order of self-assembly is now possible, as is reflected in some bizarre effects in strong flows. The tapes can be molecularly tuned to stack up to a degree limited by their tendency to twist, like plaited ribbon. When they are well-behaved at surfaces, such twisted and sometimes looped structures can be imaged by atomic force microscopy (see figure). The enormous scope for molecular design by means of peptide synthesis makes these materials interesting candidates for applications in biomimetics, drug-delivery, and rheological modification.

The peptide assembly works by means of hydrogen bonding, but with the complications of the stacking associations. One of the interesting implications of the Dutch work (*1*) is the potential synthesis of more controlled hydrogen-bonded self-assembled polymers that do not have any other interactions. Even branched structures may be included or excluded at will by the admixture of trifunctional moieties containing the same quadruple–hydrogen-bonded units. This work may help to confirm or deny some interesting recent speculations on the dynamics of branched self-assembled wormlike surfactant micelles (*6*), where even proving that the branch points exist is a challenge.

It is hard, of course, to be really pure or simple in this life, and the new self-assembling family will need to be subjected to a wider range of structural and rheological probes than has so far been possible. The authors' reference to the "history-dependent phase behavior" (*1*) of some of their materials indicates that more might be lurking beneath the benign appearance of the model fluids. It recalls another pressing question in the science of soft matter: the role of metastability. Observing no change in a complex fluid for a time scale of hours or even days is no guarantee that one has achieved equilibrium. Very long relaxations in fluid properties have been observed in ordinary polymer melts and in the self-assembled peptide tapes, as well as in more distantly related colloidal suspensions. We are very far from understanding these slow processes, but another system that can be made to exhibit them does not therefore necessarily count as a disadvantage.

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SIGNAL TRANSDUCTION

A New Player in Cell Death

Timothy Hoey

Cytokines, small proteins secreted by cells, trigger growth or differentiation in other cells. Along with hundreds of other signaling molecules, these compounds orchestrate the life of a multicellular organism by triggering varied signal transduction pathways inside cells. Most of these pathways are complex, multistep cascades of biochemical events, but cytokines trigger some of their responses with only a few intermediate steps. They accomplish this by enlisting a unique family of proteins called the STATs (*1*). What usually requires four or five proteins acting sequentially, these versatile proteins supply in one package. The STATs are able to do this because they embody features both of early steps in signaling by cell membrane-associated molecules and of the final steps, executed by nuclear transcription factors. Like many membrane molecules, STATs are regulated by phosphorylation on a tyrosine residue and have a domain specialized for interacting with other proteins containing phosphorylated tyrosines, the SRC homology 2 (SH2) domain. But like nuclear transcription factors, STATs also have DNA binding and transcriptional activation domains.

Now STATs have been shown to be required in an unexpected place—a multistep signaling pathway for the induction of cell death (apoptosis) by tumor necrosis factor–α (TNF-α). Apoptosis is initiated by activation of a cascade of proteases (the Ice family or caspases) that cleave cellular proteins, resulting in the efficient termination of the cell (*2*). On page 1630 of this issue, Kumar *et al.* report a surprising connection between STATs and TNF-induced cell death: TNF-α–induced apoptosis is defective in cells lacking STAT1 (*3*).

This lack of programmed cell death in the STAT1 mutant cells correlates with a lack of constitutive, apparently unregulated, expression of Ice family proteases. Strikingly, STAT1's participation in the apoptotic

The author is at Tularik, South San Francisco, CA 94080, USA. E-mail: hoey@tularik.com

pathway does not require the abilities for which it is best known—tyrosine phosphorylation or a functional SH2 domain. Without these functions the STAT1 mutants cannot dimerize or bind DNA; nevertheless, these mutant molecules are still critical for the regulation of cell death by TNF-α. These results point to a new activity for STAT proteins distinct from their role as cytokine-induced transcriptional activators.

Kumar *et al.* used U3A cells, a mutant cell line lacking STAT1, to explore the role of STATs in apoptosis (*4*). The cells were treated with TNF-α and actinomycin D, an inhibitor of transcription, which prevents the NF-κB–dependent activation of anti-apoptotic genes (*5*). Unlike the parental cells, STAT1 mutant cells did not die in response to this treatment. The apoptotic defect in U3A cells was reversed by introduction of the full-length STAT1 cDNA, ruling out the possibility that a mutation in another gene was responsible for the effect. One of the best characterized STAT1-activated genes, the transcription factor IRF-1, has been implicated in the regulation of apoptosis (*6*). It seemed logical that a lack of IRF-1 expression might be involved in the apoptotic phenotype of U3A cells. But when the authors tested this notion, expression of IRF-1 could not reverse the phenotype, indicating that other STAT1-regulated processes must be essential for apoptosis.

The key result in the study by Kumar *et al.* is that mutants of STAT1 lacking a functional SH2 domain or lacking tyrosine-701 were nearly as effective as the wild-type protein in restoring the apoptotic pathway. In contrast, these mutants have no activity in interferon (IFN)-induced transcriptional regulation. The SH2 domain is required for recognition of the phosphotyrosine-containing regions of the cytokine receptors as well as dimerization of STATs after their own phosphorylation. Similarly, phosphorylation of the STATs at a conserved tyrosine near the COOH-terminus is absolutely required for their dimerization and subsequent DNA binding.

The only mutation that clearly reduced STAT apoptotic activity was a point mutation at serine-727 in the COOH-terminal region. STAT1 is expressed in two alternatively spliced versions, STAT1α and STAT1β, which differ in the presence of the COOH-terminal domain. This domain functions in transcriptional activation, and serine-727 is a mitogen-activated protein (MAP) kinase substrate involved in modulating the transcriptional activity of the protein (*7*). The loss of apoptosis in these cells with a mutation at the MAP kinase substrate site is particularly intriguing because of the role that MAP kinases usually play in regulating cell proliferation. However, the activity of the COOH-terminal domain in the cell death pathway is somewhat unclear: The truncated version of STAT1, STAT1β, is similar to STAT1α in its ability to restore apoptotic signaling in U3A cells. Therefore, it seems unlikely that the COOH-terminal domain is the only effector in apoptotic STAT function.

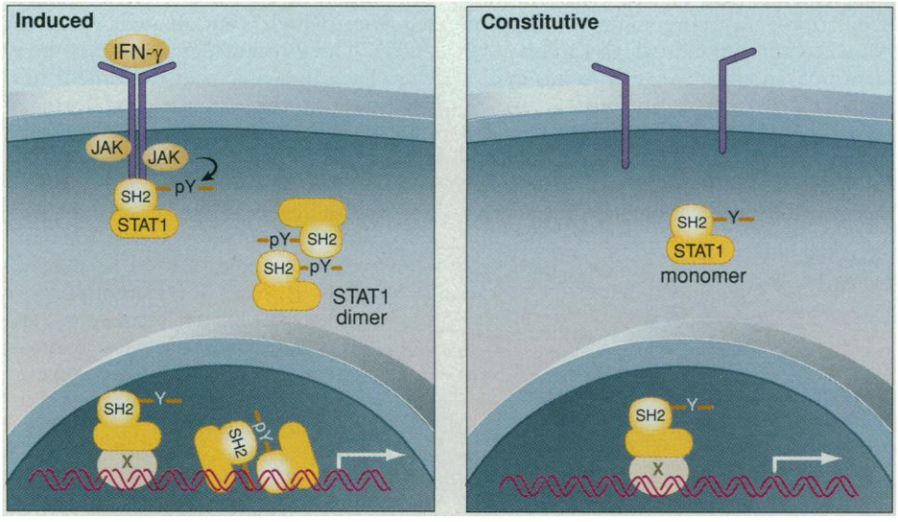
What is the mechanism underlying constitutive activation of caspase expression? Is STAT1 acting as a cytoplasmic signaling molecule or a nuclear transcription factor? One possibility is that STAT1 might function in the nucleus as a monomer without requiring DNA binding activity. In this model STAT1 would function as a coactivator, a non–DNA binding transcriptional regulator (*8*). The STAT protein would be recruited to a promoter through a protein-protein interaction with a DNA-bound partner (see figure). Consistent with this possibility, unphosphorylated STAT1 has been detected in the nucleus of unstimulated cells (*9*, *10*).

The IRF-1 protein is a good candidate for a STAT1 partner. STAT1 interacts with p48, another IRF family member, and the interaction does not require dimerization of STAT1 (*11*). Furthermore, the expression of Ice is regulated by IRF-1 (*7*), suggesting that the Ice promoter contains IRF-1 recognition sites.

In certain cells IFN-γ induces apoptosis, and Ice expression is activated by IFN-γ (*12*). This transcriptional induction of the Ice gene is correlated with tyrosine phosphorylation and DNA binding activity of STAT1. Thus, the mechanisms that send the signal further downstream in constitutive and inducible expression of STAT1 appear to be distinct. It may be that the IFN-γ induction of Ice is indirect and mediated through increased IRF-1 expression. Alternatively, the Ice promoter region may contain binding sites for STAT1 dimers.

Other models may explain the constitutive role of STAT1 in apoptosis. STAT1 could be functioning in the cytoplasm in a completely different pathway that is required for basal expression of caspases. An adapter function for STAT3, apparently as a monomer, has been implicated in the recruitment of phosphatidylinositol 3-kinase to the IFN-α receptor (*13*). Whatever the mechanism, the results reported by Kumar *et al.* imply that STAT1 has an essential function regulating gene expression as a monomer.

These results raise several interesting questions regarding the activities and regulation of STAT proteins that can be experimentally addressed. What domains of STAT1 are actually required for apoptotic function, and how do MAP kinases modulate this activity? Do other STATs have transcriptional activity as monomers, and how many other genes are constitutively regulated by STATs? The availability of knockout mice for many of the STATs will enable the isolation and characterization of new STAT-regulated genes, both constitutive and inducible.



A different way of working. Typically, STAT1 is phosphorylated on tyrosine in response to a cytokine, binds DNA, and activates transcription as a dimer (**left**). But STAT1 may also act constitutively as a monomer, recognizing a promoter through a DNA-bound protein (X) and thereby regulating gene expression (**right**).

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