sible to dissociate the PTSD from the trauma.

Each of these studies has some weaknesses, but they are countered by complementary strengths in the other studies.

Are GCs the damaging agents? Depression is accompanied by numerous physiological abnormalities, and it has not been demonstrated that the hippocampal atrophy occurs only among depressives who overproduce GCs. Moreover, among individuals with PTSD, there is no information as to the extent of the GC stress response during the trauma (or what additional physiological changes occur then). Thus, in these cases, it is not clear whether GCs mediate the atrophy. However, as noted, the defining abnormality in Cushing syndrome is GC excess, making it a likely culprit in causing atrophy.

How persistent are the changes? Although the Cushingoid atrophy reverses with correction of the endocrine abnormality (6), in the PTSD and depression studies, the atrophy occurred months to years after the trauma or the last depressive episode, and at a time when patients did not hypersecrete GCs. Thus, these long-standing changes could conceivably represent irreversible neuron loss.

The PTSD and depression studies present a problem of causality. Given the cognitive role of the hippocampus, a smaller hippocampus might be more likely to lead to being assigned frontline combat duty rather than a skilled task at headquarters. Furthermore, given the evidence of depression as a disorder of "learned helplessness," a smaller hippocampus might predispose toward depression (that is, less cognitive capacity to detect efficacious coping responses and thus greater vulnerability to learned helplessness). Finally, PTSD individuals, before joining the military, had high rates of learning disorders and delayed developmental landmarks that could reflect cerebral atrophy (*10*). Thus, a small hippocampus could be a cause, rather than a consequence, of the trauma or stressor in these studies. However, there is no plausible way in which a small hippocampus predisposes one toward the pituitary or adrenal abnormalities of the Cushingoid patients, or toward being a victim of childhood abuse.

Should this literature ultimately show that sustained stress or GC excess can damage the human hippocampus, the implications are considerable. It would then become relevant to question whether the high-dose GC regimes used to control many autoimmune and inflammatory diseases have neuropathological consequences. (Both therapeutic and experimental administration of GCs to humans results in memory impairment.) In addition, in the rodent the extent of lifetime GC exposure can influence the likelihood of "successful" hippocampal and cognitive aging (*11*); similar issues must be examined concerning our own dramatic differences in cognitive aging.

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STATs Find That Hanging Together Can Be Stimulating

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Transcription factors activate the synthesis of messenger RNAs from DNA, thereby changing the function of cells. A few years ago, a new family of transcription factors—the STATs (signal transducers and activators of transcription)—was described that mediates the action of a large and vastly important class of signaling molecules, the cytokines and growth factors. Each cytokine or growth factor activates a distinct set of genes to produce very distinct effects on the cell, yet there are only a limited number of STATs to mediate these signals. How do these few STATs generate a specific response for each cytokine or growth factor? Part of the answer to this puzzle is provided in a report by Xu *et al.* in this week's issue of *Science* (*1*).

The STATs exist as latent transcription factors in the cytoplasm. After binding of the growth factor or cytokine to its receptor, the STAT is activated by tyrosine phosphorylation (*2–4*); it then migrates to the nucleus, binds to specific DNA elements, and activates the transcription of nearby genes. The six STAT family members form homo- or heterodimers in which the phosphotyrosine of one partner binds to the SH2 (SRC homology 2) domain of the other (*5*). These dimers bind to palindromic GAS sequences that have similar affinities for different STATs.

The new work by Xu *et al.* (*1*) describes how each cytokine elicits a specific transcriptional response when each must use a limited number of factors and when the target DNA elements distinguish relatively poorly among these factors. In investigating a region of the human interferon-γ (IFN-γ) gene that contains clusters of GAS elements, these authors found that homodimers of STATs 1, 4, 5, and 6 all bind, but with different footprints. Their observations suggest that STAT dimers may cooperate in binding to clustered GAS elements and that the details of this cooperation may help to determine the cytokine specificity of the response.

The STAT proteins share blocks of homology, arrayed over their entire 800–amino acid length, and it is likely that similar domains have similar functions: (i) The SH2 domain near residue 600 is highly conserved, as is a tyrosine near residue 700, which becomes phosphorylated upon activation. In addition to binding the phosphotyrosine of another STAT, the SH2 domain also mediates the binding of STATs to specific phosphotyrosine residues of activated cytokine receptors (*6–8*). (ii) The COOH-termini of STATs mediate transcriptional activation, and phosphorylation of a serine residue in this region of STATs 1α, 3, 4, and 5 enhances this activity (*9*). In contrast, the acidic COOH-terminal region of STAT2 can activate transcription without phosphorylation (*10*). (iii) STATs contain a DNA binding domain near residues 400 to 500 (*11*). (iv) STAT2-STAT1 heterodimers bind to an additional protein, p48, to form the major transcription factor generated in response to IFN-α. The region comprising residues 150 to 250 of STAT1 interacts with p48 (*12*). Other STAT dimers may also interact with p48 (or similar proteins) to form more complex oligomeric transcription factors.

Xu *et al.* (*1*) have found a new function for the NH_2-terminal domains of STATs 1 and 4: Mediating cooperative binding of these STATs to tandem GAS sites. Deletion of 90 amino acids from the NH_2-terminus of STAT4 did not affect its binding to a single GAS site but abolished the cooperative binding of two STAT4 dimers to a double site. Furthermore, a peptide representing the

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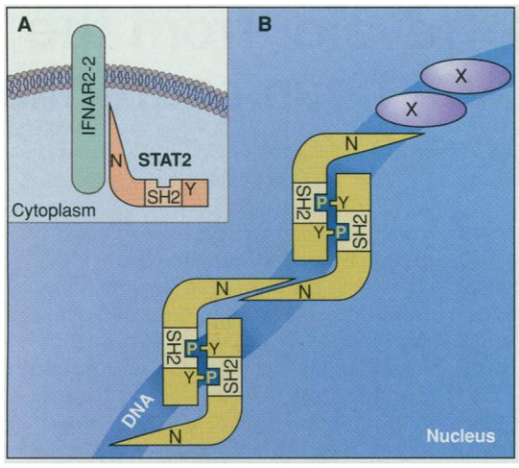

Multipurpose module: Two of the interactions mediated by NH_2-terminal domains of STATs. (**A**) The NH_2-terminal region of STAT2 assists in STAT binding to the cytoplasmic domain of the IFNAR2-2 subunit of the resting IFN-α receptor. Upon activation, the other subunit of the receptor, IFNAR1, acquires a phosphotyrosine, which binds to the SH2 domain of STAT2 (not shown) (*8*). (**B**) Interactions between NH_2-terminal domains allow STAT dimers to bind to each other on tandem GAS sites (*5*). NH_2-terminal protein-binding regions may also allow STAT dimers to interact with other transcription factors (X) at heterologous tandem sites.

NH_2-terminal 124 residues of STAT4 competitively inhibited its cooperative binding to a double site but actively stabilized its binding to a single site. Vinkemeier *et al.* (*13*) have similarly shown the importance of the NH_2-terminal region of STAT1 in mediating its cooperative binding to tandem sites.

The NH_2-terminal regions of STATs also mediate other protein-protein interactions. Deletion of 50 residues from the NH_2-terminus of STAT2 abolished its tyrosine phosphorylation in response to IFN-α (*10*). Residues 1 to 315 of STAT2 include a domain that mediates association with the IFNAR2-2 subunit of the IFN-α receptor; this association is important for the specific activation of STAT2 in response to IFN-α (*14*). In addition, the NH_2-terminus of STAT1 is important in modulating its dephosphorylation, possibly by interacting with a phosphatase (*15*). It seems that the NH_2-termini of the STATs can mediate several important protein-protein interactions, ranging from association with receptors to cooperative binding to tandem DNA elements.

We have to modify the simple idea that a single STAT dimer bound to a single GAS element is sufficient to activate transcription. As revealed by Xu *et al.* (*1*), activation of a specific gene by a particular cytokine may require the cooperative binding of STATs to several adjacent sites. As an additional example of this kind of regulation, Guyer *et al.* (*16*) have shown that IFN-γ activates a factor called γRF-1, which includes both STAT1 and a 130-kD protein, and that this factor binds to the tandem GAS sites in the promoter of the *mig* gene. Different STAT homodimers and heterodimers may cooperate on different pairs of tandem GAS sites, helping to generate enough diversity to allow each cytokine to stimulate a specific pattern of gene activation.

STAT dimers can also interact with other transcription factors. The STAT3 homodimer binds to c-*jun*, and these two factors cooperate to activate transcription (*17*); transcriptional activation of the Fcγ receptor gene requires the cooperation of STAT1 and PU.1, a myeloid and B cell transcription factor (*18*). Transcription of the c-*fos* gene is enhanced by the coordinate activation of STATs, which bind to the inducible element, and members of the ternary complex factor family (including ELK-1, SAP-1, and SAP2/ERP/NET), which bind to the adjacent serum response element in conjunction with serum response factor (*9*). This dual activation is made possible by the fact that most of the growth factors that activate STATs also activate the ERK/MAPK (extracellular signal–regulated protein kinase/mitogen-activated protein kinase) pathways, which in turn activate ternary complex factors. It remains to be seen whether the NH_2-terminal domains of STATs mediate these heterologous interactions with other transcription factors.

As convincing as the evidence for STAT-STAT interaction on tandem sites may be, further work is needed to ensure that this interaction does in fact lead to enhancement of transcription, although recent work of Yan *et al.* (*19*) is encouraging in this direction. But even now it is clear that cooperation among and between STATs and other transcription factors helps to generate enough complexity to make cytokine signals specific.

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CONDENSED MATTER PHYSICS

Calculated Clusters

Small clusters of atoms exist between the microscopic and the macroscopic: As a cluster gets bigger, it ceases being atomlike and starts behaving like bulk matter, and on the way it exhibits some very interesting properties. In particular, as the cluster grows it undergoes significant structural rearrangements and reconstructions (*1*). This transformation is manifested in various properties, such as optical (*2*) and photoelectron spectra, but a reliable way to extract cluster geometry from the data has been lacking. In a recent paper (*3*), Rubio *et al.* presented a method for obtaining the structures of small alkali metal and semiconductor clusters by comparing laboratory data with calculated spectra.

To accomplish this, they first calculate the minimum-energy ground-state geometry of the cluster. Then the dielectric response is obtained (*4*), which in turn yields the photoabsorption cross section as a function of photon energy. Rubio *et al.* found that for clusters of as little as four and six silicon atoms, a simple picture in which the electrons act independently in the absorption process failed to properly reproduce the experimental spectra. Only when they included electron interaction and screening did the calculations agree with the data. Some added surprises were found for metal clusters: for lithium, a new spectral feature above 4 eV was observed in the calculation, and for sodium, two peaks were calculated in place of the experimentally observed single broad absorption feature. The spectra for silicon also featured the optical absorption caused by quantum-confinement effects that play a role in the luminescence of porous silicon.

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