PERSPECTIVES



Multipurpose module: Two of the interactions mediated by NH,-terminal domains of STATs. (A) The NH,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 NH₂-terminal domains allow STAT dimers to bind to each other on tandem GAS sites (5). NH₂-terminal protein-binding regions may also allow STAT dimers to interact with other transcription factors (X) at heterologous tandem sites.

NH₂-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 NH₂-terminal region of STAT1 in mediating its cooperative binding to tandem sites.

The NH₂-terminal regions of STATs also mediate other protein-protein interactions. Deletion of 50 residues from the NH₂-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 NH₂-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 yRF-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 Fcy 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 ac-

tivate the ERK/MAPK (extracellular signalregulated protein kinase/mitogen-activated protein kinase) pathways, which in turn activate ternary complex factors. It remains to be seen whether the NH2-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.

References

- 1. X. Xu, Y.-L. Sun, T. Hoey, Science 273, 794 (1996). 2. C. Schindler and J. E. Darnell Jr., Annu. Rev. Biochem. 64, 621 (1995).
- 3. J. N. Ihle and I. M. Kerr, Trends Genet. 11, 69 (1995). 4 J. E. Darnell Jr., I. M. Kerr, G. R. Stark, Science
- 264, 1415 (1994). K. Shuai et al., Cell 76, 821 (1994).
- A. C. Greenlund, M. A. Farrar, B. L. Viviano, R. D. 6.
- Schreiber, EMBO J. 13, 1591 (1994)
- N. Stahl et al., Science 267, 1349 (1995)
- S. Leung, S. A. Qureshi, I. M. Kerr, J. E. Darnell Jr., 8. G. R. Stark, Mol. Cell. Biol. 15, 1312 (1995)
- L. A. Winston and T. Hunter, *Curr. Biol.* **6**, 668 (1996). S. A. Qureshi, S. Leung, I. M. Kerr, G. R. Stark, J. 10.
- . Darnell Jr., Mol. Cell. Biol. 16, 288 (1996). 11. C. M. Horvath, Z. Wen, J. E. Darnell Jr., Genes
- Dev. 9, 984 (1995) 12. C. M. Horvath, G. R. Stark, I. M. Kerr, James E.
- Darnell Jr., personal communication. U. Vinkemeier et al., EMBO J., in press
- S. Leung, X. Li, G. Stark, unpublished data
- 15. K. Shuai, J. Liao, M. M. Song, Mol. Cell. Biol., in press
- 16. N. B. Guyer, C. W. Severns, P. Wong, C. A. Feghali, T. M. Wright, J. Immunol. 155, 3472 (1995).
- 17 T. S. Schaefer, L. K. Sanders, D. Nathans, Proc. Natl. Acad. Sci. U.S.A. 92, 9097 (1995).
- C. Perez, E. Coeffier, F. Moreau-Gachelin, J. Wietzerbin, P. D. Benech, *Mol. Cell. Biol.* 14, 5023 18. (1994).
- 19. R. Yan et al., Cell 84, 421 (1996).

Calculated Clusters

CONDENSED MATTER PHYSICS_

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

SCIENCE • VOL. 273 • 9 AUGUST 1996

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.

David Voss

References

- 1. M. F. Jarrold, Science 252, 1085 (1991).
- З.
- E. C. Honea *et al.*, *Nature* **366**, 42 (1993).
 A. Rubio *et al.*, *Phys. Rev. Lett.* **77**, 247 (1996).
 X. Blase *et al.*, *Phys. Rev. B* **52**, R2225 (1995).