intrinsic membrane protein that contains multiple metal cofactors.

These studies resolve many outstanding issues, but, as with any breakthrough, they lead to several conundrums: Does FET3 or ceruloplasmin transfer the product of the enzymatic reaction, Fe(III), to the acceptor site under physiological conditions, or are these biochemical activities more indirectly related to metal-ion movement? If they are the key physiological reactions, how—and more importantly, why—is catalytic oxidation of Fe(II) to Fe(III) necessary. Having the structure may allow identification of the substrate for the ferroxidase reaction: Is it an aquo iron complex, a protein-bound Fe^{2+}, or an iron complex with a low molecular weight ligand? If it is free Fe(II), how does the ferroxidase transfer the oxidation product to the physiologically relevant acceptor protein, such as transferrin or FTR1? These naïve questions indicate that the relation between cell biology and transition metal chemistry, like that between war and love, is still enigmatic.

References and Notes

1. I. Zaitseva *et al.*, *J. Biol. Inorg. Chem.* **1**, 15 (1996).
2. R. Stearman, D. S. Yuan, Y. Yamaguchi-Iwai, R. D. Klausner, A. Dancis, *Science* **271**, 1552 (1996).
3. D. R. Dix, J. T. Bridgham, M. A. Broderius, C. A. Byersdorfer, D. J. Eide, *J. Biol. Chem.* **269**, 26092 (1994).
4. C. Askwith *et al.*, *Cell* **76**, 403 (1994).
5. D. de Silva, C. Askwith, D. J. Eide, J. Kaplan, *J. Biol. Chem.* **270**, 1098 (1995).
6. A. Dancis *et al.*, *Cell* **76**, 393 (1994).
7. M. Kammler, C. Schoin, D. Hantke, *J. Bacteriol.* **175**, 6212 (1993).
8. G. R. Lee, S. Nacht, J. N. Lukens, G. E. Cartwright, *J. Clin. Invest.* **47**, 2058 (1968).
9. Z. L. Harris *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **92**, 2539 (1995).
10. K. Yoshida *et al.*, *Nature Genet.* **9**, 267 (1995).
11. S. Osaki, D. A. Johnson, E. Frieden, *J. Biol. Chem.* **241**, 2746 (1966).
12. E. Saenko, A. Yaropolov, E. Harris, *J. Trace Elements Exp. Med.* **7**, 69 (1994).
13. Z. Harris, H. Morita, J. Gitlin, in *Multicopper Oxidases*, A. Messerschmidt, Ed. (World Scientific, Singapore, in press).
14. J. Bryson *et al.*, *Bioinorganic Chemistry of Copper*, K. D. Karlin and Z. Tyeklar, Eds. (Chapman and Hall, New York, 1993), pp.101–109.
15. G. Munson, D. Huffman, T. V. O'Halloran, unpublished results.
16. C. Collyer, J. Guss, Y. Sugimura, F. Yoshizaki, H. Freeman, *J. Mol. Biol.* **211**, 617 (1990).
17. A. Messerschmidt and R. Huber, *Eur. J. Biochem.* **187**, 341 (1990).
18. A. Messerschmidt *et al.*, *J. Mol. Biol.* **224**, 179 (1992).
19. J. W. Godden *et al.*, *Science* **253**, 438 (1991).
20. F. F. Fenderson *et al.*, *Biochemistry* **30**, 7180 (1991).
21. Y. Pan, T. DeFay, J. Gitschier, F. Cohen, *Nature Struct. Biol.* **2** (no. 9), 740 (1995).
22. R. Langen *et al.*, *Science* **268**, 1733 (1995).
23. P. Lindley, personal communication.
24. Charge distributions were calculated by P. Lindley and co-workers with the program GRASP incorporating the Del Phi algorithm [A. Nicholls and B. Honig, *J. Comput. Chem.* **12**, 435 (1991).]

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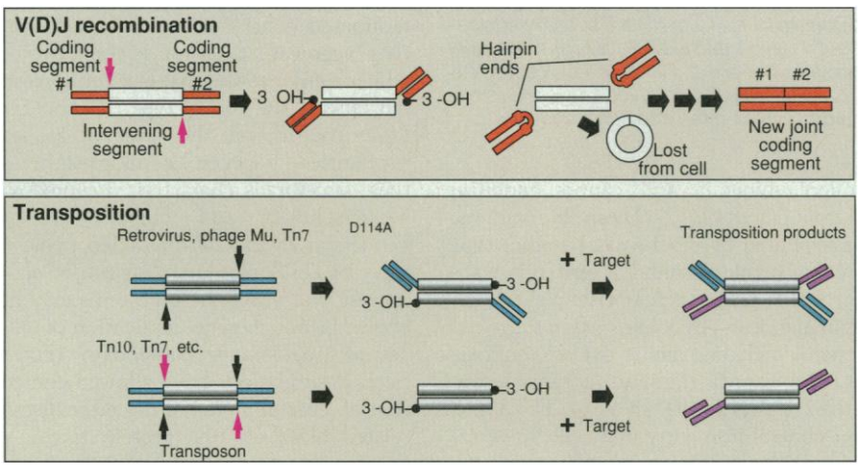
UPDATE

V(D)J Recombination and Transposition: Closer Than Expected

Nancy L. Craig

In a recent Perspective, I outlined the similarities among different transposition reactions—the movement of bacterial DNA segments and the replication and integration of certain bacteriophages and of retroviral DNA (*1*). All are mediated by recombinases of related structure that execute DNA breakage and joining by transesterification reactions. Now, in a report in this week's issue (*2*) V(D)J recombination, which underlies the ability of the immune system to assemble many different antigen-specific genes from separate gene segments, joins the family of transposition reactions.



Similarities. In V(DJ) recombination flanking DNA is joined to create a novel coding joint; in transposition the mobile segment is joined to a new target site. In retroviruses the flanking donor sequences are only several nucleotides in length.

The recombinases for both V(D)J recombination and transposition find their targets by recognition of specific DNA sequences. In V(D)J recombination, these sequences define the ends of a DNA segment that is excised to allow formation of a "coding joint"; the excised DNA segment is subsequently lost from the cell. In transposition, the mobile element, bounded by specific recognition sites, moves to a new target site.

Van Gent and co-workers (*2*) found a fundamental similarity in the chemical mechanisms of the DNA processing reactions of V(D)J recombination and strand nick, exposing a 3′-OH, which in the second step performs an intramolecular attack on the complementary strand of the nicked duplex to generate the hairpin.

This intramolecular attack proceeds by a direct transesterification: The 3′-OH exposed by the breakage step is the nucleophile that directly attacks the other strand. This reaction—direct transesterification—is the mechanistic link between V(D)J and transposition.(*3*).

The subsequent steps of V(D)J recombination—hairpin processing and joining—require other cellular proteins (*4*). Will transposition-like reactions also assemble these new coding joints?

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References

1. N. L. Craig, *Science* **270**, 253 (1995).
2. D. C. van Gent, K. Mizuuchi, M. Gellert, *ibid.* **271**, 1592 (1996).
3. K. Mizuuchi, *J. Biol. Chem.* **267**, 21273 (1992).
4. D. T. Weaver, *Trends Genet.* **11**, 388 (1995); C. B. Thompson, *Immunity* **3**, 531 (1995).