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Journal club

THE RULE OF THREE

I confess that I often don't get much out of protein structures derived from X-ray crystallography: once I see the big picture, the details don't turn me on. But this was not the case with the structure of the recombinase RecA published by Zhucheng Chen, Haijuan Yang and Nikola Pavletich in 2008.

RecA and its eukaryotic homologue, RAD51, are remarkable machines. They bind to single-stranded DNA (ssDNA) at the ends of a broken chromosome, form a filament and catalyse a search for homologous sequences elsewhere in the genome. When the filament encounters such a sequence — in yeast approximately once in 10^4 kilobases of DNA, and in mammals less than once in 10^6 kilobases (how this happens is still a mystery) — the filament engages with the double-stranded template and promotes duplex unwinding and strand exchange, thereby forming a displacement-loop intermediate that leads to DNA synthesis and to the repair of the broken chromosome.

> "homology searching is likely to proceed in triplets"

It had been known for 25 years that both ssDNA and double-stranded DNA are stretched to 1.5 times their normal B-form DNA length when bound by the recombinase, but this feature had not provided much insight into how strand exchange occurs. To address how DNA was bound by RecA, Pavletich's group linked six RecA proteins together and incubated them with a specific ssDNA, thereby creating a defined crystal. The result was a revelation: the three bases bound by each RecA monomer were maintained roughly in B-form configuration, with a large stretch in the ribose–phosphate backbone between the adjacent triplets. This finding led to the realization that homology searching is likely to proceed in triplets, an idea strongly supported by recent *in vitro* studies performed by the groups of Eric Greene, Patrick Sung and Mara Prentiss.

The American architect Louis Sullivan first expressed the idea that 'form follows function', but in this case we have learned much about the function by admiring the form.

(As I come to the end of this essay, my conscience is gnawing at me to mention another extraordinary structure–function study: the beautiful work of Dale Wigley's group in understanding the complex unwinding and cleavage activities of RecBCD.)

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