



Medical Research Council

MRC Laboratory of Molecular Biology
University Postgraduate Medical School
Hills Road, Cambridge, CB2 2QH
England

telephone Cambridge (0223) 48011

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Professor Paul Berg,
Stanford University Medical Center,
Department of Biochemistry,
STANFORD, California 94305,
U. S. A.

Dear Paul,

The chromatin picture is at the moment so exciting and so complex that it would take a full hour's lecture to set it all out. However, I can give you the main facts and ideas and also some indication as to the importance of the SV 40 minichromosomes.

As you know, Hewish and Burgoyne (B.B.R.C., 1973, Vol. 52, p. 504) published preliminary evidence which suggested that there is a repeating unit of structure in chromatin about 200 base-pairs long. Burgoyne has been here to give a lecture (he is at Mill Hill this year). Markus Noll here has started to repeat their work and has already confirmed it in outline. During the summer Roger showed that the two arginine-rich histones (F2a, and F3) form in solution, a double dimer (of the type $\alpha_2\beta_2$). There is evidence that the other two (F2a, and F2b) form either dimers, or, more likely, a hetero-dimer (of the type $\alpha\beta$). They also form higher aggregates under some circumstances.

Roger pointed out that one each of the four smaller histones is associated on the average with 100 base pairs of DNA (calculated from composition and molecular weights). He therefore proposed that there was a repeating structural unit in chromatin consisting of 200 base-pairs of DNA and two each of the four smaller histones. He also tentatively suggested that the double dimer of F2a, and F3 helped the DNA fold up into a compact structure (a bead) and that the other two histones covered the (flexible) string of DNA connecting two beads. We have further ideas along these lines but they are too speculative to set out here.

Now to come to SV 40. A lot of data suggest that the first level of structure of chromatin is a fibre about 100 Å or so in diameter (the A fibres of DuPraw) which can fold up into a tightly coiled fibre of 250-300 Å or so diameter, or greater, (the B fibres of DuPraw). Thus SV 40 is presumably the A fibre form. It contains the four smaller histones but not F1, which, incidentally, is not necessary for the X-ray pattern.

To interpret the structure of the A fibre we need to know the "contraction ratio". This is the ratio of the length of DNA in an A fibre/length of the A fibre. This is the figure you measure as 9 or 10. At this point we do some special pleading. Fibres of chromatin show a strong repeat of about 110 Å in the fibre direction. If the fibre is

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F₂
F_{2a}
2^a
2^b
F₃

100 Å

made very dry a strong 75-80 Å reflection appears. We assume

- (1) the 110 Å corresponds to the A fibre structure
- (2) that an A fibre shrinks in length when it dries in about the ratio 110/80.

We assume that what you see in the e. m. for SV 40 is the dry structure and we deduce that the wet concentration ratio is thus in the region of 6 or 7. All this is done to identify the 110 Å reflection as the size of the hypothetical unit in the fibre direction, since 200 base-pairs are 680 Å long and if fitted into a repeat of 110 Å give a contraction ratio of about 6.2. As you can see the argument is suggestive but somewhat insecure.

Thus what we want to know first about SV 40 is

- (1) the contraction ratio dry
- (2) the contraction ratio wet (by cross-linking?)
- (3) the number of strands of DNA.

I think the last point is obvious. Naturally, the naked SV 40 DNA is a single double-helical DNA, lightly supercoiled. But is what you see in the e/m a folded circle, or is the circle first folded to be a figure of eight which is then folded on itself to give a double circle and then folded on a small scale with the histones.

Your horse-shoes are relevant here. If they consist basically of an intact unbroken circle of DNA, is the naked region a single double-helix (as we have been assuming) or a pair of double-helices (as in the folded figure of eight type model).

We should also like to have a slightly better figure for the diameter of the fibre (130 Å? 100 Å?) and whether, as the photos superficially suggest, the fibre is "hollow". Finally, there are complicated arguments about twist, but I think these are best left on one side.

I have just heard from Jack Griffith saying that he thinks England is too cold for a visit and that instead he plans to go to sunny Spain with "a Swedish friend", so we may not see him after all. This is a pity as there is far more to say than what I've set out here. However, I hope this gives you some idea of what we'd like to learn from SV 40. Incidentally, Roger's hypothesis predicts that there should be equal amounts (on a molar basis) of the four smaller histones in SV 40, which is not exactly supported

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by the recent evidence, so further data on this point would be very welcome.

Do let me know if you would like clarification of the above or further information. Odile and I planted a rose hedge on Monday (it was a little cold). Otherwise, I spend my time studying tennis balls.

Best wishes,

Yours ever,
Francis

F.H.C. Crick