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Somatic Hybridization as a Tool for the Study of Differentiation: a Review

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Somatic hybridization is rapidly establishing itself as the equivalent of bacterial mating systems in metazoan cell biology. In recent years several groups have successfully used human-mouse hybrid cells to demonstrate linkages between human genes and to allocate such genes to their chromosomes. Another field in which somatic hybridization seems to be destined to become a major tool of enquiry is the investigation of the mechanisms controlling the expression of differentiated functions. In general, the problem has been approached by crossing an 'undifferentiated' cell line with one that, derived from a 'differentiated' tumour, expresses some of the specific characteristics of the

tissue of origin. A number of systems have been studied in this manner, including high activities and inducibility of certain enzymes, the synthesis of certain tissue-specific products and the electrical membrane properties of neurons (Davidson & Yamamoto, 1968; Davidson & Benda, 1970; Schneider & Weiss, 1971; Minna, Nelson, Peacock, Glazer & Nierenberg, 1971; Bloom, Choi & Lamb, 1971). The same approach has been used to investigate virus-mediated transformation (Basilico & Wang, 1971) and malignancy (Harris, Miller, Klein, Worst & Tachibana, 1969). It is concluded that the expression of differentiated functions in hybrids may depend, not only on the genetic make-up of these cells and the mode of regulation studied, but also on the extent to which the latter is intact in the 'differentiated' parent and the tissue of origin of the 'undifferentiated' parent. Recent experiments have demonstrated the possibility of studying the control mechanisms and genetics of such properties that are extinguished on hybridization with an 'undifferentiated' cell line through the use of human-mouse hybrid cells (Klebe, Chen & Ruddle, 1970). Such hybrids may re-express the differentiated function on loss of certain human chromosomes. If it is possible to cross diploid mouse cells isolated directly from their tissue with heteroploid human cell lines and if such cells lose human chromosomes, the latter approach may be greatly expanded.

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STEROID BIOCHEMISTRY GROUP COLLOQUIUM ON 'STEROIDS AND CHROMATIN'

Chromatin Structure

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The complexity of chromosome structure in eukaryotes has been one of the obstacles to extrapolation from prokaryotes of knowledge on mechanisms of transcription and replication. In

recent years new impetus to work on chromatin structure has resulted from a better understanding of histone structure and the molecular structure of the deoxyribonucleohistone complex. This, together with continuing studies on both the structure of chromatin as seen by electron microscopy and the function of chromatin as revealed by studies *in vitro* with cell-free preparations, has produced some

information of value. This communication attempts to summarize present findings.

Eukaryotic chromosomes are composed of DNA, histones and non-histone ('acidic', 'residual') proteins. DNA and histones occur in relatively equivalent and, at least for DNA, in constant amounts per nucleus. Histones in all species examined vary little from the five types: lysine-rich histone F1, slightly lysine-rich histone F2b and arginine-rich histones F2a1, F2a2 and F3 (Butler, Johns & Phillips, 1968). Amino acid sequences are known for histones F2b (Iwai, Ishikawa & Hayashi, 1970) and F2a1 (DeLange, Fambrough, Smith & Bonner, 1969; Ogawa *et al.* 1969) and part sequences for histone F1 (Rall & Cole, 1970).

On the basis of knowledge about proteins for which complete structures are known (Prothero, 1966; Schiffer & Edmundson, 1967), the sites of α -helix in histones F2b and F2a1 have been predicted and suggestions for their structural arrangement in the deoxyribonucleohistone complex have been made (Richards & Pardon, 1970; Boublik, Bradbury & Crane-Robinson, 1970).

X-ray-diffraction studies of fibre and gel specimens of deoxyribonucleoprotein indicated that the DNA in the complex is coiled (deoxyribonucleoprotein supercoil) into a regular structure with pitch 120 Å and diameter 100 Å. At very low concentrations in solutions lacking bivalent ions the deoxyribonucleoprotein supercoil appears to be absent. As the deoxyribonucleoprotein concentration increases, or on the addition of Mg^{2+} ions (concentration above 1 mM), the supercoil appears, indicating that some of the forces responsible for generation of this configuration may be inter-molecular. Intramolecular forces are very important in maintaining the supercoil, since partial removal of histone by dissociation of the complex in salt (sodium chloride at above 1.2 M concentration or magnesium chloride at above 0.3 M concentration) results in the loss of supercoiling and successful reconstitution of the complex from histones is dependent on the method by which the protein was prepared. The supercoil configuration is, however, the form in which most and possibly all the DNA of the eukaryotic chromosome is to be found.

Molecular models constructed from space-filling CPK (Ealing Corporation, Cambridge, Mass., U.S.A.) components can be built to investigate the likely arrangement of the histone on the supercoiled DNA. The model for histone F2a1 gives a value of 0.88:1 for the mass ratio protein/DNA, which agrees with the calculated value for native nucleohistone lacking histone F1, when histone F2a1 is attached only in the large groove of the DNA. This implies that access for sequence-recognizing molecules might be via the small groove in the DNA. Further

implications of the model for the mechanics of genetic de-repression will be discussed.

Electron microscopy of cell nuclei and metaphase chromosomes shows that chromatin consists of 'unit' threads having a diameter of approx. 170–250 Å in sectioned (Davies, 1968) or thread preparations in the presence of bivalent ions, and approx. 100 Å in preparations treated with chelating agents (Ris, 1969).

In the electron microscope the absence of water prevents the deoxyribonucleohistone complex from assuming the supercoil configuration. Thus direct comparison between the results of electron microscopy and X-ray diffraction of wet specimens is not possible.

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Control of Transcription of Chromatin Deoxyribonucleic Acid

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The mechanism of protein synthesis appears to be basically similar in many forms of life. However, the composition of DNA and the control of the expression of its genetic information for protein synthesis varies considerably between eukaryocytes and prokaryotes. Apart from being present in large amounts, the DNA of mammalian cells is heterogeneous in its composition, since it contains sequences that are highly repetitious and those that are not (Britten & Kohne, 1968). In addition, in eukaryotes the DNA is complexed with protein to form chromosomes that are housed in the nucleus separate from the protein-synthesizing machinery of the cytoplasm. The differentiated cells of an