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Formation and Function of Polyribosomes in the Early Embryonic Development

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It has been shown that in the eggs of several animals the rate of protein synthesis is very low before fertilization, i.e. there is a small number of active polyribosomes. After fertilization the rate of protein synthesis increases rapidly and this is accompanied by a concurrent rapid build-up of polyribosomes (Rinaldi & Monroy, 1969; Firtel & Monroy, 1970). There is evidence that the structural state of the ribosomes of the unfertilized egg prevents their interaction with mRNA (Maggio, Vittorelli, Caffarelli-Mormino & Monroy, 1968). It is known that until approximately the blastula stage most of the protein synthesis is directed by mRNA that was synthesized during oogenesis (summary in Monroy, 1965). Nevertheless from the earliest post-fertilization stages some heterogeneous rapidly labelled RNA, which is neither rRNA nor tRNA, is synthesized and becomes associated with polyribosomes; most of this rapidly labelled RNA is found in a class of small polyribosomes (Rinaldi & Monroy, 1969; Kedes & Gross, 1969; Firtel & Monroy, 1970), which are the ones most sensitive to actinomycin (Infante & Nemer, 1967; Firtel & Monroy, 1970). Contrary to earlier assumptions (Spirin & Nemer, 1965) these polyribosomes are not inactive in protein synthesis; in fact there is evidence that they are the site of the synthesis of histones (Nemer & Lindsay, 1969; L. H. Kedes & P. R. Gross, personal communication; M. Crippa, personal communication). In the early stages of development the largest percentage of the new (i.e. of zygotic origin) mRNA thus appears to be translated by the small polyribosomes. Data on amphibians (Crippa & Gross, 1969) and on sea urchin (M. Crippa, personal communication) show that only about 50% of the total amount of mRNA present in the young embryo (cleavage stages to early blastula)

is associated with polyribosomes. DNA-RNA hybridization experiments suggest that both in the amphibians (M. Crippa & E. Costantino-Ceccarini, personal communication) and in the sea urchin (M. Crippa, personal communication) mRNA may be stored in rapidly sedimenting heavy particles. The molecular hybridization technique is being applied in an attempt to determine how the mRNA that is synthesized during oogenesis is stockpiled and rendered untranslatable in the unfertilized egg.

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The Function of Polyribosomes Attached to Membranes in Animal Cells

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The role of the membrane-bound polyribosomes in the synthesis of protein for export from animal cells is well established. In addition to facilitating the passage of protein from the cell, the containment of the protein within the membrane of the endoplasmic reticulum has other advantages. Thus in the assembly of immunoglobulin G from light chains and heavy chains the controlled environment provided by the membranes is important for the interaction of the four chains (Williamson, 1969).

Brew (1969) has described the role of membranes in the synthesis of lactose by the mammary gland. Thus α -lactalbumin is synthesized by the membrane-bound polyribosomes, released to the cisternal space (Brew & Campbell, 1967) and passed to the Golgi apparatus, where *N*-acetyl-lactosamine synthetase is located (Coffey & Reithel, 1968; Fleischer, Fleischer & Ozawa, 1969). The α -lactalbumin changes the substrate specificity of this enzyme and lactose is synthesized (Brew, Vanaman & Hill, 1968).

There is a marked variation in the rate of metabolic turnover of the proteins of the endoplasmic reticulum (see e.g. Kuriyama, Omura, Siekevitz & Palade, 1969; Arias, Doyle & Schimke, 1969). In particular there is a differential effect on the activity

of various enzymes, such as NADPH-cytochrome *c* reductase and cytochrome *b*₅, which are associated with the endoplasmic reticulum, after the administration of phenobarbitone to rats. This suggests that polyribosomes do not lay down a membrane with a certain fixed spectrum of enzymes but that there is an addition and deletion of the proteins of the membrane. These studies *in vivo* are in accord with the work of Ragnotti, Lawford & Campbell (1969), who showed that various preparations of isolated polyribosomes from liver made NADPH-cytochrome *c* reductase and that the newly synthesized enzyme became associated with the membranes.

There have been many recent attempts to determine whether the membrane-bound polyribosomes of the adult liver cell effect the synthesis of proteins that are retained by the cell as well as those destined for export. A fraction rich in polyribosomes, which from electron microscopy seems to be free of fragments of the rough-surfaced endoplasmic reticulum, can be isolated from rat liver (Blobel & Potter, 1967). Since these polyribosomes are not apparently associated with membrane they are termed free polyribosomes. To determine whether the latter are functionally distinct from the membrane-bound polyribosomes the synthesis of specific proteins by the two fractions *in vitro* has been studied. Redman (1969) reports that the free polyribosomes synthesized 7–20 times as much ferritin, a protein retained by the cell, as did membrane-bound polyribosomes (see also Hicks, Drysdale & Munro, 1969). The failure of isolated free polyribosomes to effect the synthesis of albumin

has been reported by Takagi & Ogata (1968) and of glycoproteins by Hallinan, Murty & Grant (1968). One of the difficulties in this work is the satisfactory characterization of the newly synthesized protein (see e.g. Schreiber, Rotermund, Maeno, Weigand & Lesch, 1969). With this proviso it seems right to conclude that the adult liver cell contains two types of functionally active polyribosomes and that certain of the proteins retained by the cell are not synthesized by the membrane-bound polyribosomes.

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COMMUNICATIONS

Model Building Studies on the Structure of Deoxyribonucleohistone

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Sequence studies on purified histone fractions are in progress in other laboratories. We have used the published sequence for fraction IV (DeLange, Fambrough, Smith & Bonner, 1969) as the basis for an atomic-space-filling model comprising a single molecule. Possible conformations of the molecule have been investigated for the histone molecule free from and also in complex with DNA.

A highly compact globular conformation is possible in which most of the hydrophobic residues readily lie in the centre of the molecule giving an overall diameter of approx. 50 Å. The distribution

of basic residues on the surface is such that this conformation is a most unlikely one for the histone in the nucleohistone complex. Similarly the fully extended chain is another unlikely conformation. The model readily permits 5–8 turns of α -helix, giving a proportion of 18–30%, which is not incompatible with experimental observations (Oriel, 1966; Bradbury, Crane-Robinson, Goldman, Rattle & Stevens, 1967).

In the complex between histone and DNA the following considerations have been taken into account.

- (1) The number of electrostatic bonds formed between basic residues of the histone molecule and charged phosphate groups of DNA is maximized.
- (2) All possible secondary structure within the histone molecule is permitted.
- (3) The histone is accommodated as far as possible in either groove of the DNA double helix.