Appearance of Rapidly Labeled, High Molecular Weight RNA in Nuclear Ribonucleoprotein

RELEASE FROM CHROMATIN AND ASSOCIATION WITH PROTEIN*

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Chromatin and nuclear ribonucleoprotein (nRNP) have been prepared from a human carcinoma cell line. Following a 1-hour [3H]uridine pulse, 60 to 70% of the nuclear radioactivity, after removal of nucleoli, was found in the chromatin, the balance in nRNP. This was true whether the chromatin and nRNP were separated by velocity centrifugation or by isopycnic centrifugation on Metrizamide gradients. Radioactivity in chromatin and nRNP was found in high molecular weight RNA, with mean sedimentation coefficients of 20 S and 15 S, respectively, as determined on sodium dodecyl sulfate-sucrose gradients. Experiments on the kinetics of appearance of radioactivity in the RNA of the two fractions suggest that some of the chromatin-associated RNA is precursor to nRNP-RNA.

The proteins of nRNP are complex as revealed by sodium dodecyl sulfate gel electrophoresis. The contamination by chromatin protein was estimated to be 5%. Experiments involving short pulses of [3H]tryptophan, and pulse-chase, suggested that the rapidly turning over proteins of nRNP were not complexed with RNA while still associated with chromatin. However, it was also shown that the radioactivity in nRNP following short pulses of [3H]tryptophan did not correspond to the major bands seen on stained sodium dodecyl sulfate gels. It is therefore concluded that the protein of nRNP consists of two classes, species present in large amounts, possibly common to all RNA in nRNP, which are relatively stable and may be complexed to RNA still associated with chromatin; and a large number of rapidly turning over species, each present in small amounts and associated with nRNP only after its release from chromatin.

Eukaryotic heterogeneous nuclear RNA can be isolated complexed with protein. Initial reports indicated that protein in nuclear ribonucleoprotein preparations was of limited heterogeneity (1, 2), but other work has demonstrated that if care is taken to isolate nRNP without extensive degradation of the RNA, a more complex protein complement is found (3–6). The electrophoretic pattern of these proteins is tissue-specific (5).

Although it has been reported that all of the hnRNA can be isolated free of chromatin in the form of nRNP (5, 7), we have found that in cultured colonic carcinoma cells a considerable proportion of uridine pulse-labeled nuclear RNA is associated with chromatin, and some of this appears to be precursor to species isolated as nRNP. Because it has been demonstrated that protein is complexed to the RNA transcript while still associated with chromatin (8–11), we investigated whether protein isolated as nRNP is found first associated with the chromatin fraction. Our results indicate that the rapidly turning over proteins in nRNP are added to the nRNP only after its release from chromatin. However, it was also found that following a short pulse of [3H]tryptophan, the radioactivity in nRNP did not correspond to the major protein species seen as bands on SDS gels, but was distributed fairly uniformly throughout the gel. This suggests that the proteins of nRNP consist of a large number of species with rapid turnover rates which are present in small amounts, as well as stable species present in larger amounts. In contrast to the rapidly turning over proteins, the stable species may be complexed with RNA while the transcript is still associated with chromatin.

MATERIALS AND METHODS

Cell Culture—HT-29 cells were used in all experiments. This is an epithelial cell line established by Fogh from a primary adenocarcinoma of the colon of a 44-year-old human female. It is hypertetraploid. HT-29 cells were obtained from Dr. Fogh at passage 134 and have been maintained in this laboratory for 2 years. All experiments were done on cells of passage 165 to 180.

The cells were grown in Eagle’s Minimum Essential Medium, containing 15% fetal calf serum in Falcon plastic flasks with a surface area of 75 cm². They were split 1:3 every 4 to 6 days and were split 1:2 when used for an experiment. They were usually confluent by day 4, at a density of 1.3 x 10⁶ cells/cm². The cells continue to grow rapidly at this time, a 1-hour [3H]thymidine pulse labeling 52% of the cells.
Incorporation of either uridine or tryptophan was linear for up to 1 each preparation. The high salt DNase digestion procedure described by Soeiro and method of Spirin Darnell (14), and run on SDS-sucrose gradients according to Derman Densi-Flow, and the refractive index was measured with a Zeiss once by vortexing in 5 ml of Hanks' solution, then resuspended in 4 ml rinsed once with Hanks' solution and scraped into Hanks' solution, and Pederson (12). All procedures were carried out at 4'. The cultures were was from New England Nuclear Co. Recovery of DNA in nuclei was 94% (83 to 100%, 10 experiments). However, nuclear DNA in the nRNP fraction ranged from 3% to 100%. However, nuclear DNA in the nRNP fraction was not released by addition of 25 mM EDTA before Triton X-100 did not change the results (data not shown). The chromatin and nRNP pellets were resuspended in 0.01 M sodium phosphate buffer, pH 7.0; 0.1% SDS; and 0.1% β-mercaptoethanol and then dialyzed overnight against this buffer. It is not necessary to remove nucleic acid prior to electrophoresis (12, 19, 20). The banding pattern of the stained gels was highly reproducible. The gels were calibrated with the following standards: bovine serum albumin M, -66,500; ovalbumin, M, -45,000; lactoglobulin, M, -35,000; sheep β-hemoglobin, M, -16,073; sheep α-hemoglobin, M, -16,047. For counting, gels were cut into 1 mm slices with a razor blade. Each slice was covered with 0.1 ml of H2O2 and digested in a sealed scintillation vial at 45° until dissolved (usually 30 to 40 hours). Aquasol, 10 ml, (New England Nuclear) plus distilled H2O (5%) was added to each vial. Recovery of counts applied to the gel was greater than 90%.

Scintillation Counting—All samples were counted in 10 ml of Aquasol plus distilled H2O (5%) in an Intertechnique scintillation counter. Efficiency was monitored by external standard ratio. In all cases, a minimum of 1500 counts were counted.

Analytical Procedures—For determination of specific activity of protein and RNA, aliquots of each fraction were precipitated at 4° by addition of an equal volume of 0.6 N perchloric acid, and washed twice with cold 0.2 N perchloric acid. Protein was determined on this precipitate by the method of Lowry et al. (21). RNA was extracted by the method of Scott et al. (22) and assayed by the orcinol method (23). DNA was assayed according to Burton (24).

RESULTS

Incorporation of [3H]Uridine into Nuclear Fractions—We consistently observed that following a 15-min or 1-hour pulse of [3H]uridine, approximately 60% of the nuclear radioactivity, after removal of nuclei, was found in the chromatin fraction and the balance in the nRNP fraction, which is the post chromatin supernatant. All of the radioactivity was alkali-labile and therefore not in DNA, all of which was alkali-stable (0.5 N NaOH, 1 hour, 37°). The radioactivity in the chromatin fraction was not released by addition of 25 mM EDTA before pelleting the chromatin, nor was it an artifact of the inclusion of Triton X-100 in the preparation of nuclei, since omission of Triton X-100 did not change the results (data not shown). The radioactivity in the chromatin fraction was due to contamination by nuclei (and hence ribosomal RNA) since nuclei were removed during preparation. In addition, carrying out the uridine pulse in the presence of 0.04 μg/ml of actinomycin D, which specifically inhibits nuclear RNA synthesis (25), did not change the distribution of radioactivity between the chromatin and nRNP fractions. When the isolated chromatin was resuspended in Buffer A, and respun through 60% sucrose as described, only 7% of the radioactivity was found in the supernatant (nRNP fraction). Similarly, when an aliquot of the post chromatin supernatant (nRNP) was added to unla- beled nuclei, and the isolation procedure was again carried out, 86% of the radioactivity was again isolated in the nRNP fraction. The 1 hour pulse-labeled RNA in the nRNP had a
mean sedimentation coefficient of 15 S on SDS-sucrose gradients, with some material running up to 20 S (Fig. 1). In three separate experiments, the chromatin-RNA similarly labeled was somewhat larger, with a mean coefficient of about 20 S, and material running up to 30 S (Fig. 1).

A second method of fractionation, sedimentation of the post nuclear supernatant on Metrizamide-buoyant density gradients, gave consistent results. Cells were labeled for 4 days with [1^C]thymidine and 1 hour (or 15 min, not shown) with [3^H]uridine. Fig. 2 shows that 60% of the [3^H] was found in the same region of the gradient as [1^C]thymidine-labeled chromatin. The remainder, found at higher densities, was presumably in free nRNP.

Relationship between RNA of Chromatin and nRNP— Cultures of cells were labeled continuously with [3^H]uridine for periods of from 30 s to 60 min. Fig. 3 illustrates that with a 30 s pulse, 100% of the radioactivity in the nucleus (after removal of nucleoli) was in the chromatin fraction, and none in the nRNP. By 90 s, radioactivity appeared in the nRNP fraction, with a corresponding decrease in the percentage found in chromatin. At 2 min, only 70% of the radioactivity was in chromatin, the balance was found in the nRNP. The relative amounts remained essentially constant up to 60 min, although the percentage found in nRNP may have slowly increased. Fig. 4 shows that the specific activity of the RNA in chromatin rose very quickly, while the increase was slower in the nRNP-RNA. These results suggest that some of the chromatin-RNA is precursor to the RNA isolated in nRNP.

Presence of Protein in nRNP—Fig. 5 shows the results of CsCl2 gradients of formaldehyde-fixed nRNP. The buoyant density of the RNA in nRNP was 1.43 (Fig. 5A), similar to what has been previously reported (1, 3, 5), and corresponding roughly to an RNP consisting of 80% protein. The same results were obtained for 1 min uridine pulse-labeled RNA in the nRNP fraction (not shown). Fig. 5B illustrates that at least 85% of the tryptophan-labeled protein was found at the same buoyant density and was therefore complexed to RNA. The small amount of apparently free protein in this gradient (density < 1.36) could have been due to incomplete fixation, or reversal of fixation during long centrifugation (26). These results indicate that the tryptophan-labeled protein in the nRNP was firmly associated with the RNA, since it has been recently shown that, at least in chromatin, it would otherwise not be fixed by formaldehyde treatment (27).

Size Distribution of nRNP—Following a 1-hour [3^H]uridine pulse, radioactivity in the nRNP fraction (post chromatin supernatant) sedimented between 1 S and 200 S with a modal value of about 76 S (Fig. 6A). When the RNP was isolated by centrifugation of the post chromatin supernatant, resuspended, and run on an identical sucrose gradient to that in Fig. 6A, the size distribution was not as broad (Fig. 6B). The modal value is a sharper peak at somewhat less than 76 S, and there is far less material sedimenting at larger S values. Finally, Fig. 6C shows that some labeled RNA of small size was not
systems (1,2,4,5). Although the resolving power of one-dimen-
sional gels is limited, these results point to a marked heteroge-
neity of the proteins of nRNP. The complete absence of histones in the nRNP preparation
should be noted. The small, low molecular weight peaks in nRNP clearly ran slightly behind the two
separate preparations shown. The major nRNP band ran at a
molecular weight of about 34,000, in close agreement with the
molecular weight of the major protein of nRNP in other
systems, respectively. These patterns were highly reproducible.

This preparation had been simultaneously labeled for 1 hour
with [14C]tryptophan. We can see that the post chromatin
supernatant contained a great deal of tryptophan-labeled protein at the top of the sucrose gradient (Fig. 6A) which did
not pellet with the nRNP (Fig. 6B), but was, rather, found in the corresponding supernatant (Fig. 6C). This has previously
been identified as the soluble nuclear protein fraction (28). In several experiments with [3H]tryptophan incorporation, where
the counts were considerably higher and proper quantitation
could be made, we found that 60 to 65% of the [3H]tryptophan-
labeled material in the post chromatin supernatant pelleted
with the nRNP. As noted, the CsCl, gradient shown in Fig. 5B
suggests that all of the protein pelleted with the nRNP is firmly
associated with it (27).

Characterization of Protein of nRNP—Fig. 7, A and B are
scans of stained SDS gels of nRNP and chromatin prepara-
tions, respectively. These patterns were highly reproducible.
The complete absence of histones in the nRNP preparation
should be noted. The small, low molecular weight peaks in nRNP, which appear to be histone contaminants, are not. This
is shown in the gel photograph in Fig. 7C. The small molecular weight proteins in nRNP clearly ran slightly behind the two
low molecular weight histone bands of chromatin in the two
separate preparations shown. The major nRNP band ran at a
molecular weight of about 34,000, in close agreement with the
molecular weight of the major protein of nRNP in other
systems (1, 2, 4, 5). Although the resolving power of one-dimen-
sional gels is limited, these results point to a marked heteroge-
neity of the proteins of nRNP.

Since our preparation of chromatin and nRNP seems to

Fig. 5. CsCl, isopycnic gradient centrifugation of formaldehyde-
fixed nRNP labeled for 1 hour with: A, 2 µCi of [3H]uridine/ml, or B, 4
µCi of [3H]tryptophan/ml.

Fig. 6. Sucrose gradient centrifugation of: A, the postchromatin
supernatant; B, the nRNP pellet resuspended in Buffer A; C, an
aliquot of the post nRNP supernatant. Cells were labeled for 1 hour
with 5 µCi of [3H]uridine, O—O, and 1 µCi of [14C]tryptophan,
O—O, per ml. The gradients were 15 to 30% sucrose in Buffer A.
Centrifugation was for 15 hours at 15,000 rpm in the Beckman SW-41
rotor at 4°. The arrow indicates the position of the monosome peak
from an aliquot of the cytoplasm made 0.5% in SDS and run on an
identical gradient.

Fig. 7. SDS gel scans where the radioactivity from labeled
nRNP from a pulse and pulse-chase experiment was run on stained SDS gels. It is important to note that the
radioactivity did not correspond to the positions of the bands in stained gels (Fig. 7, A and B), but was more uniformly
distributed throughout the gel. This was particularly apparent in
the nRNP.

Although the high molecular weight species of chromatin
showed a relatively higher level of incorporation at 5 min, this
was not true of nRNP (Fig. 10A). In nRNP, these proteins
showed a higher level of incorporation only after 30 min (Fig.
10C), while the distribution of label remained the same in
chromatin from 5 to 30 min. However, Fig. 11, A to C illustrate that during a chase with unlabeled tryptophan, the distribution
of radioactivity in nRNP (or chromatin), did not change.
Hence, these high molecular weight labeled proteins of nRNP
could, again, not have been associated first with chromatin and
then shifted to nRNP.
Fig. 7. SDS gel electrophoresis of proteins of nRNP and chromatin. A, scan of nRNP; B, scan of chromatin; C, photograph of duplicate gels of nRNP (left) and chromatin (right).

Fig. 8. Specific activity of proteins in: whole cell, ■■■■; nuclei, ●●●●; nRNP, △--△; and chromatin, ▲▲▲▲. Cells were labeled for various times with 4 μCi of [3H]tryptophan/ml in Hanks' solution.

DISCUSSION

Our data indicate that rapidly turning over high molecular weight RNA can be isolated associated with chromatin and that some of this RNA is precursor to RNA found in nRNP. Monahan and Hall (29) have reported that precursor to hnRNA is found in chromatin isolated on Metrizamide gradients. This is consistent with the recent observations that globin sequences can be found in the chromatin-associated RNA from mouse fetal liver cells (30) and that the RNA content of chromatin is greatest in material isolated from tissues with the highest capacities for RNA synthesis (31, 32), although in the latter reports, the nature of the RNA is unknown.

In assessing the problem of RNA breakdown in our preparation, it should be noted that the rapidly labeled RNA of both our chromatin and nRNP is not as large as the RNA that can be obtained from whole nuclei (33). Indeed, the RNA that we extract from HT-29 nuclei is larger than either chromatin or nRNP RNA (>50 S). Clearly, therefore, there is RNA breakdown during preparation, but this must be limited to nicking, since we routinely recover all of the nuclear radioactivity...
during subsequent fractionation. Monahan and Hall (29) obtained RNA from their chromatin and nRNP preparations which was about the same size as that reported here, despite the presence of an RNase inhibitor. Hence, breakdown of nuclear RNA during rather lengthy subnuclear fractionations may be unavoidable, perhaps due to the close association of the RNA with nucleases involved in its processing. It should not, however, be assumed that nicking of chromatin RNA is sufficient for its release from chromatin. If the presence of pulse-labeled RNA in our nRNP fraction were simply due to breakdown, we would not have obtained the results of Fig. 3, where it was shown that increasing the length of pulse resulted in a progressively greater percentage of the nuclear RNA in the nRNP fraction as nRNP (both the 1 min and the 1 hour pulse-labeled RNA in the nRNP fraction had a buoyant density in CsCl of 1.43). Richardson (34) has recently pointed out that even in the transcription of free DNA, very little is known about the attachment of RNA to DNA and the mechanism of its release. In fact, denaturation of the polymerase can permit hybridization of up to 600 nucleotides of the bound RNA to superhelical bacteriophage DNA (34). Tata and Baker (35) have reported that in rat liver the bulk of the rapidly labeled RNA of the nucleus is associated with chromatin, and have suggested that some processing (polyadenylation) occurs at the site of synthesis (36).

The relative amounts of incorporated \( ^{3}P \)uridine remain constant at about 70% in the chromatin and the balance in nRNP, with pulse times of from 2 to 60 min (Fig. 3). One might have expected radioactivity to continue accumulating in the nRNP fraction, presumably as chromatin RNA is synthesized and released. However, this same distribution has been seen by others and by us in human fibroblasts in culture. Similarly, it is not clear why the specific activity of the RNA in nRNP does not continue to increase rapidly from 30 to 60 min (Fig. 4). It is undoubtedly true that RNA in both fractions consists of a large number of species with a wide range of turnover rates (and perhaps functions). Indeed, some chromatin-RNA is surely not precursor to nRNP-RNA and may remain associated with chromatin (37–39). In addition, not all hnRNA in chromatin may be quickly released, as suggested for RNA of certain temperature-induced puffs of Drosophila (40); and some hnRNA of intermediate stages in processing may be relatively stable (41). On consideration, then, it is clear that the results obtained depend on a highly complex series of events in a mixed population of RNA, and are difficult to predict or extensively interpret.

Our data are consistent with published observations that hnRNA is associated with protein which is quite heterogeneous (3–6) rather than one or two distinct species (1, 2). Recently, Pederson (5) has suggested that at least some of the major protein species of nRNP may be common to all (or most) RNA in nRNP.

More than 85% of tryptophan-labeled material in isolated nRNP migrates in the same position in CsCl as nRNP (Fig. 5B) and therefore does not represent free protein. Recent experiments on chromatin suggest that because this protein is fixed to the RNA by formaldehyde, it represents protein firmly associated with RNA (27). It would be desirable to demon-

\*J. Karn, G. Vidali, and V. Allfrey, personal communication.
strate more conclusively that all protein in nRNP is pelleted only because of its association with RNA. One way would be to show that ribonuclease digestion of RNA in the post chromatin supernatant eliminates any pelleting of protein upon subsequent isolation of nRNP by centrifugation (see "Methods"). However, we have found, as have others (1, 42) that not all of the RNA in nRNP is susceptible to digestion by nuclease and therefore a macromolecular, protein-containing complex might still exist. In addition, we have observed, as have others, (1) that after RNAse digestion of nRNP, the protein precipitates. Therefore, although the nRNP protein is not found in the 122,000 × g supernatant after ribonuclease digestion, it no longer forms a discrete pellet, but rather is recovered from the walls of the centrifuge tube.

A very important question is how much of the nRNP-protein is chromatin contamination. The nRNP contains an average of 6% of the nuclear DNA. However, when the cells were labeled with [3H]thymidine, 47% of the radioactivity in nRNP pellet was found to be DNA, (density > 1.6) when the formaldehyde-fixed nRNP was spun on CsCl (as compared to 2% and 7% when the labeling was with [3H]uridine and [3H]tryptophan, respectively). Therefore, of the 6% of the total nuclear DNA in nRNP, almost half is essentially protein-free, and the protein-associated DNA (DNAp) in nRNP is only 3% of the total nuclear DNA. One can consider the amounts of RNA in nRNP and chromatin to be roughly equal (following a 1-hour pulse of [3H]uridine, the specific activity of nRNP-RNA is about 60% of that of chromatin-RNA, and the nRNP fraction contains about 60% of the radioactivity in chromatin). Therefore the ratio of nuclear DNA to nRNP-RNA DNA in nRNP is 20 (just as it is for chromatin-RNA). However, only 3% of the DNA is present in nRNP as DNAp, so the ratio of DNAP to RNA in nRNP is 0.6. This chromatin present in nRNP has a protein to DNA ratio of 1 (using histone, Fig. 7). Because the protein to RNA ratio in nRNP is about 4, the contamination due to chromatin proteins in nRNP is 

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\frac{1}{4} \times 0.6 \times 100 = 15%.
\]

This calculation can be done in another way. When the actual total protein to DNA ratio in nRNP is measured, it is found to be variable, as expected, since DNA is a contaminant. The values range from 5:1 to 17:7:1 (six determinations) with an average of 9:7:1. However, 50% of this DNA is protein-free, so the true ratio of chromatin protein to total DNA in nRNP is 1 (protein:DNA of histone-free chromatin) × 0.5 = 0.5. The average chromatin protein contamination is therefore the true ratio of chromatin protein to DNA in nRNP divided by the measured ratio of total nRNP protein to DNA: 0.5/9.7 × 100 = 5%, and, similarly, ranges from 3% to 10%. Some of these assumptions are approximations, but the contamination of nRNP with chromatin protein does not seem to be sufficiently high to change the interpretation of the data presented. Perhaps, the most straightforward indication of limited contamination is the completely different labeling patterns of the proteins in the two fractions (Figs. 10 and 11).

In considering our data from the pulse and pulse-chase experiments (Figs. 8 and 9), we do not know the rate of synthesis, cytoplasmic (or nuclear) pool sizes, or rate of transport of the protein in the nRNP and chromatin fractions. These results should therefore be approached cautiously. Nevertheless, in no case did we obtain results which would indicate that most of the rapidly turning over nRNP protein is complexed to the transcript during synthesis or when the transcript is otherwise associated with chromatin. It should be noted however, that observations of Beermann (43), on puffs of the giant chromosomes of Chironomus, suggested that protein did become associated with RNA to form RNP while still associated with chromatin. This observation has been repeated in the Balbiani rings and other puffs of Diptera tissue (8, 44-46), the loops of lampbrush chromosomes (47-49) and, most recently in regions of mammalian chromatin active in RNA synthesis (9). Furthermore, Scott and Sommerville (11) have shown that proteins isolated from RNP released into the nucleoplasm are antigenically similar to nonbasic proteins of lampbrush loops. We have recently obtained evidence which suggests that proteins which protect a portion of the RNA of both chromatin and nRNP from nuclease digestion are similar.

Our results, however, are not inconsistent with this previous work on the presence of nRNP in chromatin, since we have also shown that following short pulses of [3H]tryptophan, the radioactivity in nRNP does not correspond to the major bands on stained SDS gels. We suspect, as already stated by Georgiev (1), Stevens and Swift (8), and Berendes (40), that these stable proteins, present in large amounts and therefore possibly common to all hnRNA (5), bind to growing transcripts and are involved in packaging and transport (1, 8, 40), while the rapidly turning over proteins are added later, and we suggest, are involved in processing. Enzymes capable of cleaving hnRNA (51) and adding poly(A) to hnRNA have been identified in nRNP (52).

There is, in fact, evidence that protein added to RNA still associated with chromatin is stable. Pelling (53) has shown that RNA-synthesizing structures in Chironomus puffs are not labeled with radioactive amino acids up to 2 hours after label injection, and Clever (45) has shown that the same products, present in large amounts and therefore possibly common to all hnRNA, bind to growing transcripts and does not turn over significantly for up to 28 days. Furthermore, inhibitors of protein synthesis do not affect the structure of lampbrush loops (45) or the initial induction of puffs by edysone (45, 55), though subsequent puff formation, also dependent on RNA synthesis (30), is inhibited.

We have also shown that the major chromatin proteins do not turn over rapidly. This is consistent with several reports that much (non-histone) chromosomal protein exhibits great stability (56, 57).

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