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Transcriptional Regulation in Avian Erythroid Cells†

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ABSTRACT: Both the translational and transcriptional repertoires of nearly mature avian erythroid cells appear to be highly restricted: molecular hybridization experiments demonstrate the presence of about 4000 species of poly(A)$^+$ nRNA and fewer than 100 species of poly(A)$^+$ mRNA. This paper addresses the question of whether the nRNA of erythroid cells contains sequences which, although not expressed in the erythroid cells, are found on polysomes in another cell type. We have prepared cDNA from liver mRNA and have determined the representation of liver mRNA sequences in the erythroid cell nRNA. Liver mRNA consists of about 14000 species of poly(A)$^+$ RNA. Of these only about 100 species are detectable in erythroid cell nRNA. The vast majority of liver mRNA species is undetectable in erythroid cells; i.e., they are present at less than 0.03 copies per cell. The few species of liver mRNA that are detectable in erythroid cells are present in both the nuclear and polysomal RNA at concentrations less than 0.1 copies per cell. These data suggest that gene expression in avian erythroid cells is highly regulated at the transcriptional level.

Messenger RNA populations are developmentally regulated; that is, some RNA species are present on polysomes of one cell type but absent from those of another cell type (Galau et al., 1976; Ryffel & McCarthy, 1975; Axel et al., 1976). Such developmental regulation could result from selective transcription or from posttranscriptional selection among primary transcripts. Recent work with sea urchin embryos has suggested that the major control point in developmental regulation may be posttranscriptional. Although some polysomal mRNA species are stage specific in sea urchin embryos, the hnRNA[1] populations of different stages are experimentally indistinguishable (Kleene & Humphreys, 1977; Wold et al., 1978).

In this paper we examine transcriptional and posttranscriptional sequence selection in avian erythroid cells. These cells are well suited for such experiments, since they contain about 4000 species of poly(A)$^+$ hnRNA but only about 100 species of poly(A)$^+$ mRNA (Lasky et al., 1978). The specific question we address here concerns the erythroid cell hnRNA sequences that do not appear on erythroid cell polysomes: do these molecules contain sequences that appear on polysomes in another cell type?

We have approached this question by using cDNA complementary to liver mRNA. Our results show that, of the approximately 14000 mRNA sequences in liver mRNA, a maximum of 100 are found in the hnRNA of erythroid cells. This suggests that gene expression in avian erythroid cells is highly regulated at the transcriptional level.

Materials and Methods

Isolation of Liver Poly(A)$^+$ mRNA, Erythroid Cell hnRNA, and Erythroid Cell Poly(A)$^+$ mRNA. Polysomal poly(A)$^+$ mRNA was isolated from liver tissue as described by Axel et al. (1976), except that the liver was minced and homogenized in a loose-fitting Dounce homogenizer. Polysomal material was isolated by centrifugation at 26000 rpm for 2 h at 4 °C in a Beckman SW27 rotor through a linear 10–40% sucrose gradient in 25 mM NaCl, 5 mM $MgCl_2$, and 25 mM Tris-HCl, pH 7.5. The gradients were collected through a flow cell, and the absorbance was monitored at 260 nm. Material sedimenting more rapidly than 100 S was pooled and precipitated with ethanol. The precipitated polysomes were then treated with 25 mM EDTA for 20 min at 0 °C. Material sedimenting more slowly than 80 S after EDTA release was isolated by centrifugation at 26000 rpm for 3.5 h at 4 °C in a Beckman SW27 rotor. Poly(A)$^+$ mRNA was isolated by oligo(dT)-cellulose chromatography as described previously (Lasky et al., 1978). Erythroid cell hnRNA and poly(A)$^+$ mRNA were isolated from anemic chickens as previously described (Lasky et al., 1978).

Preparation of Liver cDNA and "Selected Liver cDNA". Single-stranded DNA complementary to liver poly(A)$^+$ mRNA (liver cDNA) was prepared as described by Efstradiatis et al. (1975). RNA-dependent DNA polymerase from avian myeloblastosis virus was provided by Life Sciences, Inc., through the Viral Oncology Branch of the National Institutes of Health. The specific activity of the liver cDNA was (4–6) $\times 10^6$ cpm/μg.

To isolate "selected liver cDNA", we hybridized liver cDNA to excess erythroid cell hnRNA to R_0t = 250 M s in 0.5 M

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[1] Abbreviations used: nRNA, nuclear RNA; hnRNA, heterogeneous nuclear RNA; poly(A)$^+$, poly(A)-containing; EDTA, ethylenediaminetetraacetate; NT, nucleotide; R_0t, the product of RNA concentration, in moles of nucleotides per liter, and time, in seconds; PB, an equimolar mixture of Na_2HPO_4 and NaH_2PO_4.

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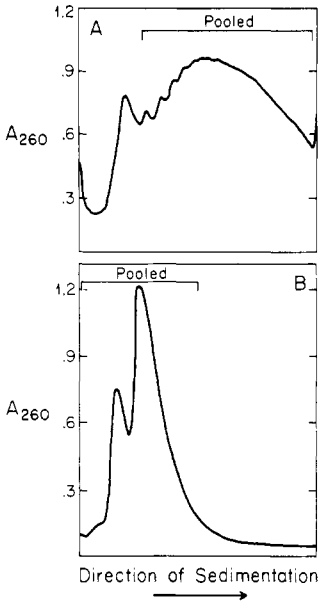

FIGURE 1: (A) Sedimentation of liver polysomes. Pelleted liver polysomes (140 A_{260} units) were sedimented through linear 10–40% sucrose gradients. Sedimentation was for 2 h at 4 °C and 26 000 rpm. The gradients were collected through a 2-mm flow cell, and the indicated region was pooled and precipitated with ethanol. (B) Sedimentation of EDTA-released ribonucleoprotein particles. EDTA-released ribonucleoprotein particles were sedimented through linear 5–20% sucrose gradients. Sedimentation was for 3.5 h at 4 °C and 26 000 rpm. The gradients were collected through a 2-mm flow cell, and the indicated region was pooled and precipitated with ethanol.

PB. This is equivalent to R_0t = 560 M s in 0.2 M PB (Britten et al., 1974). Selected liver cDNA was isolated by hydroxyapatite chromatography and subsequent centrifugation in alkaline sucrose, as described by Benz et al. (1977).

RNA–cDNA Hybridization. Hybridization of cDNA to RNA was performed as described previously (Lasky et al., 1978) in 0.2 M PB. Concentrations of poly(A)$^+$ RNA were determined by hybridization to [^{3}H]poly(U) (Miles) (Bishop et al., 1974). The kinetics of hybridization were analyzed by using the computer program of Britten et al. (1974), as modified by R. B. Goldberg.

Results

Preparation of cDNA Complementary to Liver mRNA. Since the nRNA populations of two cell types are likely to be more similar than their mRNA populations, we thought it particularly important to avoid hnRNA contamination of the heterotypic (liver) mRNA (Kleene & Humphreys, 1977; Wold et al., 1978). We therefore isolated poly(A)$^+$ mRNA from liver polysomes after dissociation with EDTA. The cDNA transcribed from this RNA represents the poly(A)-contiguous (or 3′) regions of the mRNA. As long as the 3′ regions of liver mRNA are not repeated more often in the genome than the 5′ regions, the conclusions of the hybridization experiments reported here are unaffected by the length of the cDNA probe. EDTA release was therefore the preparative method of choice, despite the partial degradation of the mRNA (see below).

Figure 1A shows the size distribution of polysomes from liver. Although the ribonuclease content of chicken liver is reportedly high (Axel et al., 1976), the polysomes appear undegraded. The modal number of ribosomes per polysome is about 8, suggesting an average mRNA length of about 1200 nucleotides (NT). Material sedimenting faster than monosomes was pooled and dissociated with EDTA. The EDTA-released polysomes were then fractionated by sedimentation, and the expected subunit distribution was obtained (Figure 1B). Material sedimenting more slowly than 80 S was pooled, and the poly(A)$^+$ RNA was isolated by chromatography on oligo(dT)–cellulose and analyzed by sedimentation in denaturing sucrose gradients (data not shown). The mean size of the poly(A)$^+$ liver mRNA was 500 NT, indicating that degradation occurred, presumably during the EDTA release. The cDNA transcribed from liver poly(A)$^+$ mRNA had a number-average length of approximately 300 NT.

Table I: Hybridization of Liver cDNA to Excess Erythroid Cell hnRNA[a]

method of assaying hybrids	R_0t[b] (M s)	% reactable cDNA hybridized
(A) S1 nuclease resistance	560	21
	560	19
	530	14
(B) hydroxyapatite chromatography	550	13
	680	16

[a] cDNA [2000 cpm (400 pg)] complementary to liver mRNA was incubated in 5 μL of 0.5 M PB, 0.1% $NaDodSO_4$, and 1 mM EDTA for 24 h with 1 mg/mL of hnRNA. The fraction of the cDNA resistant to S1 nuclease was determined as described under Materials and Methods. In each experiment the fraction of the cDNA that was nuclease resistant after a 24-h incubation in the absence of RNA (1–5%) was subtracted from the nuclease resistance in the presence of RNA. The fraction of the cDNA that was nuclease resistant was then normalized to the amount of cDNA driven into hybrid by excess liver mRNA after incubation to R_0t = 100 M s (70–90%). Hydroxyapatite chromatography was performed as described by Benz et al. (1977). [b] Corrected to R_0t in 0.2 M PB by using the salt correction factors of Britten et al. (1974).

Liver mRNA Sequences in Erythroid Cell hnRNA. The presence of liver mRNA sequences in erythroid cell hnRNA was examined by hybridization of cDNA transcribed from poly(A)$^+$ liver mRNA to an excess of total erythroid cell hnRNA. This hybridization was carried to R_0t (corrected to 0.2 M PB) = 500–600 M s, sufficient to detect erythroid cell hnRNA sequences present at only 0.03 copies per cell. After hybridization to high R_0t, 14–21% of the hybridizable liver cDNA became resistant to S1 nuclease (Table I). The extent of hybridization measured by hydroxyapatite chromatography was approximately the same as that measured by S1 nuclease resistance, indicating that the homology between erythroid cell hnRNA and liver cDNA extends over the whole length of the hybridized cDNA molecules. Analysis of the thermal denaturation of these hybrids, using S1 nuclease resistance, showed that the heterotypic hybrids are well matched, with a melting temperature of 82 °C in 0.2 M PB (0.3 M Na^+; data not shown).

The concentration of liver mRNA sequences in erythroid cell hnRNA can be determined from the kinetics of hybridization of liver cDNA to erythroid cell hnRNA. To increase the precision of these measurements, we isolated liver cDNA that was complementary to erythroid cell hnRNA; we term this cDNA "selected liver cDNA" (Figure 2). When the selected liver cDNA was hybridized back to total erythroid cell hnRNA to R_0t = 1000 M s, about 78% was S1 nuclease resistant. When the selected liver cDNA was hybridized to erythroid cell poly(A)$^+$ hnRNA, about 46% became S1 nuclease resistant at R_0t = 300 M s (the highest R_0t attained in our experiments with poly(A)$^+$ hnRNA). Thus, only about 60% (46/78) of the liver mRNA sequences in total erythroid cell hnRNA is detectable in erythroid cell poly(A)$^+$ hnRNA.

We have previously shown that poly(A)$^+$ hnRNA from immature avian erythroid cells consists of two concentration classes, with 25 RNA species present at 80 copies per cell and

Table II: Hybridization of Selected Liver cDNA to Erythroid Cell RNA

RNA population	fraction of total selected liver cDNA in each component	fraction of hybridizable selected liver cDNA in each component	$R_0t_{1/2}$ (obsd) (M s)	concn of each 1200 NT RNA species in the population[a] (molecules/cell)
(A) poly(A)$^+$ hnRNA (1 component)	0.46	0.67	25	0.08
(B) poly(A)$^+$ hnRNA (2 components)	0.11	0.16	1.2	1.5
	0.35	0.52	32	0.06
(C) poly(A)$^+$ mRNA	0.55	0.82	30	0.08

[a] The concentration of each RNA species was calculated from the ratio of the $R_0t_{1/2}$ for rabbit (α + β)globin cDNA to the $R_0t_{1/2}$(observed) for the RNA population considered. We use the following figures for these calculations: $R_0t_{1/2}$ (rabbit globin) = 4.5 × 10^{-4} M s; average size of poly(A)$^+$ hnRNA = 1200 NT; number of poly(A)$^+$ hnRNA molecules per erythroid cell = 4000; and number of poly(A)$^+$ mRNA molecules per erythroid cell = 5000.

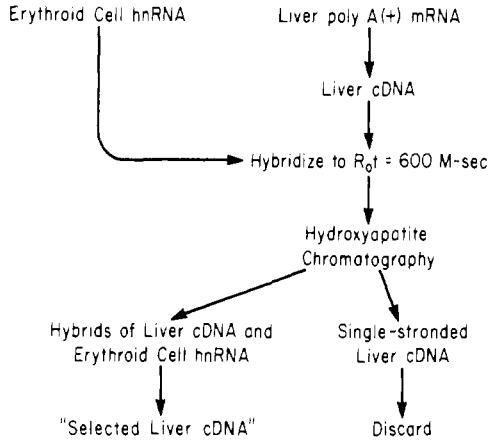

FIGURE 2: Preparation of selected liver cDNA.

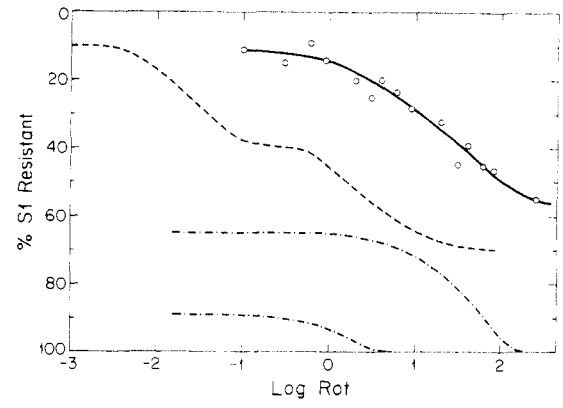

FIGURE 3: Hybridization of selected liver cDNA to erythroid cell poly(A)$^+$ hnRNA. Hybridization was performed in 0.2 M PB, 0.5% $NaDodSO_4$, 2mM EDTA, at 70 °C. RNA concentrations were determined by [^{3}H]poly(U) hybridization as described by Bishop et al. (1974). Hybrids were assayed by resistance to S1 nuclease. (—) Hybridization of erythroid cell poly(A)$^+$ hnRNA to selected liver cDNA; (-·-·) analysis of hybridization into two kinetic components; (- - -) hybridization of erythroid cell poly(A)$^+$ hnRNA to cDNA transcribed from it (Lasky et al., 1978).

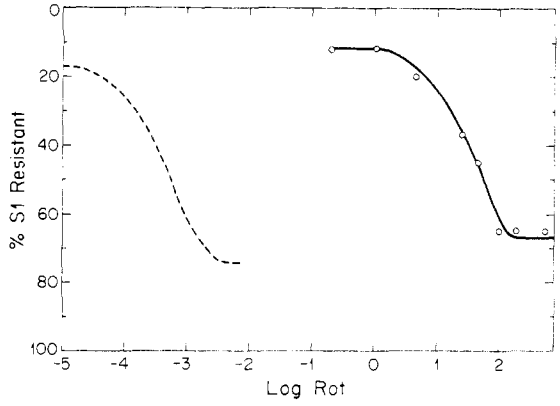

FIGURE 4: Hybridization of selected liver cDNA to erythroid cell poly(A)$^+$ mRNA. (—) Hybridization of selected liver cDNA to erythroid cell poly(A)$^+$ mRNA; (- - -) hybridization of erythroid cell poly(A)$^+$ mRNA to cDNA transcribed from it (Lasky et al., 1978).

about 4000 species present at about 0.5 copies per cell (Lasky et al., 1978). In contrast, polysomal poly(A)$^+$ RNA from these cells contains fewer than 100 species (Lasky et al., 1978). In order to determine whether the abundant and rare poly(A)$^+$ hnRNA molecules included liver mRNA sequences, we studied the kinetics of hybridization of selected liver cDNA to erythroid cell poly(A)$^+$ hnRNA (Figure 3).

If the data of Figure 3 are considered as a single kinetic component, the curve-fitting program gives $R_0t_{1/2}$(observed) = 25 M s. Alternatively, when the data of Figure 3 are analyzed assuming two kinetic components, we find that the more abundant component comprises 11% of the selected liver cDNA and hybridizes with $R_0t_{1/2}$(observed) = 1.2 M s and the rare component comprises 35% of the selected liver cDNA and hybridizes with $R_0t_{1/2}$(observed) = 32 M s. The root mean square error of the one-component fit is 0.040, whereas the root mean square error of the two-component fit is 0.035.

Under the conditions used in this experiment, rabbit (α + β)globin cDNA hybridizes to the mRNA from which it was transcribed with $R_0t_{1/2}$ = 4.5 × 10^{-4} M s. The complexity of rabbit (α + β)globin mRNA is about the same (1200 NT) as the length of the average poly(A)$^+$ hnRNA molecule isolated from these cells (Lasky et al., 1978). We have used the hybridization of rabbit globin mRNA to its cDNA as a kinetic standard in order to determine the fraction of a given RNA population driving each component of the selected liver cDNA. If the data of Figure 3 are considered as a single kinetic component, we conclude that each liver mRNA sequence is present in poly(A)$^+$ erythroid cell hnRNA at 0.08 copies per cell. When we assume two kinetic components, we conclude that each RNA species in the first class is present in erythroid cell poly(A)$^+$ hnRNA at 1.5 copies per cell and each species of the second class is present at 0.06 copies per cell.

Liver mRNA Sequences on Erythroid Cell Polysomes. We next addressed the question of whether the selected liver mRNA sequences were restricted to the nuclei of erythroid cells or were also found on erythroid cell polysomes. We hybridized selected liver cDNA with erythroid cell poly(A)$^+$ mRNA, which had been prepared from EDTA-released polysomes (Figure 4 and Table IIC). The extent of hybridization of selected liver cDNA to erythroid cell poly(A)$^+$ mRNA was similar to the extent of hybridization to total hnRNA from these cells. The selected liver cDNA hybridized to poly(A)$^+$ mRNA as a single kinetic component with $R_0t_{1/2}$-

Table III: Hybridization of Total and Selected Liver cDNA to Liver mRNA

	fraction of cDNA in each component	$R_0t_{1/2}$(obsd) (M s)	concn of each species (molecules/ cell)	$R_0t_{1/2}$(pure) (M s)	no. of RNA species[a]
(A) total liver cDNA					
(1)	0.21	9.5×10^{-3}	3800	2.0×10^{-3}	11
(2)	0.26	0.12	300	0.031	170
(3)	0.36	7.2	5	2.6	14000
(B) selected liver cDNA					
(1)	0.57	0.24	150		

[a] The number of liver mRNA species in each class was calculated by using 1800 NT as the average size of liver mRNA (Axel et al., 1976).

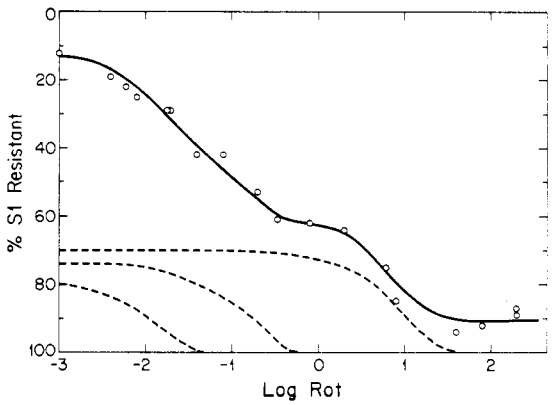

FIGURE 5: Hybridization of liver poly(A)$^+$ mRNA to cDNA transcribed from it. (—) Hybridization of unselected liver cDNA to liver poly(A)$^+$ mRNA; (- - -) analysis of hybridization into three kinetic components.

(observed) $\doteq$ 30 M s. We calculate that each of the liver mRNA species represented in selected liver cDNA is present in erythroid cell polysomes about 0.08 times per cell.

Representation in Liver mRNA of RNA Sequences Common to Liver and Erythroid Cells. In order to compare the concentrations of common mRNA sequences in liver and erythroid cells, we measured the hybridization kinetics of liver poly(A)$^+$ mRNA to total cDNA transcribed from liver mRNA and to selected liver cDNA. Unselected liver cDNA hybridized to liver poly(A)$^+$ mRNA over a wide range of R_0t values, indicating at least three concentration classes of liver mRNA sequences (Figure 5 and Table IIIA). The sizes and complexities of these classes are given in Table III and are in approximate agreement with those reported by Axel et al. (1976).

In contrast to the hybridization of unselected liver cDNA, selected liver cDNA hybridizes to poly(A)$^+$ liver mRNA as a single kinetic component, with kinetics corresponding to those of the liver mRNA sequences present at intermediate concentrations (Figure 6 and Table IIIB). The selected liver cDNA comprises 18% of the hybridizable liver cDNA, and the intermediate class of liver cDNA comprises 31% of the hybridizable liver cDNA (26% of the total liver cDNA). Since all the selected cDNA hybridizes with the same kinetics as the intermediate class of unselected liver cDNA, we infer that the sequence complexity of the selected liver cDNA is about 60% that of the intermediate class liver mRNA, or about 100 species.

Discussion

Regulation of mRNA Populations in Nonerythroid Cells. In general, a comparison of the mRNA populations of two different cell types reveals both shared and unshared species. Using a single-copy DNA probe for the complex class of mRNA, Galau et al. (1976) showed that different but partially overlapping sets of rare mRNAs are expressed in different developmental stages of the sea urchin. Using cDNA probes, Ryffel & McCarthy (1975) and Axel et al. (1976) demonstrated both shared and unshared mRNA sequences in different tissues of mice and chickens. Hastie & Bishop (1976), however, concluded that all the mRNAs of one cell type are present in another cell type, albeit at differing concentrations.

More of the genome is represented in hnRNA populations than in mRNA (Getz et al., 1975; Hough et al., 1975; Bantle & Hahn, 1976; Herman et al., 1976; Kleiman et al., 1977; Levy & McCarthy, 1976; Levy et al., 1976). In contrast to mRNA populations, the hnRNA populations of different developmental stages of the sea urchin are experimentally indistinguishable (Kleene & Humphreys, 1977; Wold et al., 1978). In the sea urchin rare mRNAs specific to a particular developmental stage are expressed in the hnRNA populations of all other stages examined (Wold et al., 1978). In the rat, although much more of the genome is represented in brain hnRNA than in liver or kidney hnRNA, all the sequences expressed in kidney and liver hnRNA are also found in brain hnRNA (Chikaraishi et al., 1978). There is no information about the presence of tissue-specific mRNAs in heterotypic hnRNA in the rat, but globin mRNA sequences have been detected in mouse liver and brain, as well as in uninduced Friend erythroleukemia cells (Humphries et al. 1976; Gilmour et al., 1974).

The present accumulated evidence supports a cascade model of gene regulation (Scherrer, 1973). Up to 30% of the genome is transcribed into nRNA, of which only a fraction is processed, exported, and translated. In contrast to the apparent transcriptional promiscuity of sea urchins, transcription in vertebrates seems to be at least partly tissue specific (Chikaraishi et al., 1978; Lasky et al., 1978). Nearly mature erythroid cells, for example, contain only about 4000 species of poly(A)$^+$ hnRNA, representing less than 1.4% of the chicken genome.

Transcriptional Selectivity in Avian Erythroid Cells. In the work reported here we have addressed the question of whether erythroid cell hnRNA contains RNA sequences that are found on polysomes in another cell type. We chose liver as a source of heterotypic mRNA because it contains a large diversity of mRNA species, indeed a substantial fraction of the maximum number of genes that can be maintained with a reasonable genetic load (Ohta & Kimura, 1971). An additional reason for choosing liver as a source of mRNA for these experiments was the finding of Axel et al. (1976) that most liver mRNA species are also present in oviduct mRNA. In view of this latter report, we were surprised to find that fewer than 100 liver mRNA species are detectable in erythroid cell hnRNA.

Most of the liver mRNA sequences found in erythroid cells are present in erythroid cell poly(A)$^+$ hnRNA at about 0.06 copies per cell (Table II). In contrast, the previously detected rare species of erythroid cell poly(A)$^+$ hnRNA are present at

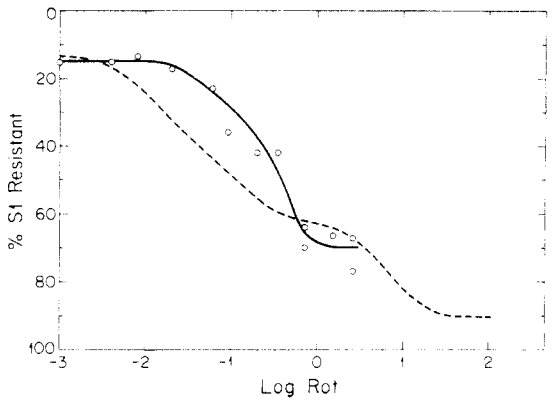

FIGURE 6: Hybridization of selected liver cDNA to liver poly(A)$^+$ mRNA. (—) Hybridization of selected liver cDNA to liver poly(A)$^+$ mRNA; (---) hybridization of unselected liver cDNA to liver poly(A)$^+$ mRNA from Figure 5.

about 0.5 copies per cell (Lasky et al., 1978). This situation differs from that in other cell types, where rare species of poly(A)$^+$ hnRNA (detected by cDNA hybridization) and of total hnRNA (detected by single-copy DNA hybridization) are present in similar concentrations (Herman et al., 1976; Hough et al., 1975; Chikaraishi et al., 1978). In sea urchins both translated and untranslated potential mRNA sequences of the rare class are present in hnRNA at about one copy per cell (Wold et al., 1978). The low concentrations of these sequences may be due to a low level of constitutive transcription or to a subpopulation of cells, either nonerythroid cells or less mature erythroid cells. The absence of the majority of liver mRNA sequences, however, suggests that general transcriptional leakage is unlikely. Cellular heterogeneity seems to us the more likely explanation of the low level of expression of most of the liver mRNA sequences in the erythroid cell population we studied.

The vast majority of liver mRNA sequences, however, are undetectable in erythroid cell hnRNA in these experiments. They are therefore present in erythroid cell hnRNA at less than 0.03 copies per cell (our limit of detection), that is, at less than 6% the concentration of the previously reported rare poly(A)$^+$ hnRNA species. This low level can reflect (1) a low rate (or absence) of transcription, (2) a rapid exit to the cytoplasm, or (3) a high rate of intranuclear degradation (Tobin, 1978). We favor the first explanation—transcriptional control. The second explanation, preferential export of liver mRNA sequences, seems unlikely since it would require the additional hypothesis of rapid and specific turnover of liver mRNA or of highly selective translation. The third possibility, intranuclear degradation, cannot be formally excluded but would require that the half-life of transcribed but unprocessed sequences be less than the time required to transcribe an average structural gene, i.e., far less than the half-life we have determined for the bulk of erythroid cell hnRNA (Tobin et al., 1978). Rapid intranuclear degradation of transcripts containing liver mRNA is thus experimentally indistinguishable from low (or no) transcription. We feel that the most reasonable interpretation of the data is therefore that the absence of the vast majority of liver mRNA sequences in erythroid cell hnRNA is the result of transcriptional control.

We conclude that transcription in avian erythroid cells is more selective than in other cell types that have been examined. The erythroid cell population with which we have worked consists primarily of postmitotic, terminally differentiated cells. These cells synthesize RNA more slowly and have lower levels of RNA polymerase than other cell types (Tobin et al., 1978; Longacre & Rutter, 1977). The decrease in transcriptional activity during avian erythropoiesis is coextensive both with the gradual replacement of histone H1 by histone H5 and with a change in the composition of nonhistone chromosomal proteins (Appels et al., 1972; Vidali et al., 1973; Moss et al., 1973). Thus, the striking transcriptional selectivity of nearly mature avian erythroid cells, although initially surprising, is consistent with the unique state of their chromatin and with their penultimate position in erythropoiesis.

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