Studies on Highly Metabolically Active Acetylation and Phosphorylation of Histones*

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SUMMARY

The capacity to effectively label tumor cell histones using very short pulses of $[^3H]acetate and $[^32P]phosphate (1 to 10 min) has been developed. Four histone fractions $F_1$, $F_{sal}$, $F_{26}$, and $F_6$, are extensively acetylated in short time periods. About 70% of the acetate accumulated on the histone during a short pulse is removed with a half-life of ~3 min. The rest of the metabolically active acetate is removed with a half-life of 30 to 40 min. Histones $F_{sal}$, $F_{26}$, and $F_6$ are acetylated at the NH$_2$-terminus and this modification is metabolically stable. In short pulses, histones are labeled with $[^3P]$ in the order $F_{26} > F_6 > F_S > F_{sal}$ > $F_1$. All fractions have a fairly rapid turnover time ($t_{1/2} = 20$ to 40 min) except $F_1$ phosphate which turns over some 5 times more slowly.

Histones are an unusual group of proteins in that they are modified extensively by acetylation, phosphorylation, and methylation (1, 2). Histones $F_1$ and $F_6$ are phosphorylated extensively in dividing cells, $F_6$ is phosphorylated slightly in interphase cells, but extensively in metaphase (3, 4). $F_6$ is apparently not phosphorylated in mammalian somatic cells, although it, along with the other histone molecules, is extensively phosphorylated during spermatogenesis in trout (5, 6). Histones $F_1$ and $F_26$ are phosphorylated quite rapidly after synthesis in trout testes, but $F_{sal}$ is phosphorylated much more slowly in a process which does not begin until 24 hours after synthesis.

In mammalian cells, Alfrey and colleagues have observed acetylation in the arginine-rich histones $F_{sal}$ and $F_2$ (7, 8) and the sites of acetylation have been established by the sequence analyses of DeLange et al. (9, 10). More recently McCarty and co-workers (11) indicated that histones $F_{sal}$ and $F_{26}$ from duck erythrocytes were also capable of being acetylated, in agreement with the work of Candeias and Dixon who made similar findings in trout (12-14). Dixon and his co-workers (15) and Shepherd et al. (16, 17) have argued that a substantial degree of acetylation occurs on newly synthesized histone, although Sanders et al. (11) have shown that acetylation can occur in avian erythrocytes at a time when histone synthesis is essentially nonexistent.

Three histone molecules are acetylated at the NH$_2$-terminus and this is thought to be a highly stable modification (1). Sites of internal acetylation have been documented in the work cited above, and this acetate appears to turn over. Analysis of the preceding work indicates that the turnover of acetate at internal positions is quite rapid, and it is possible to conclude from the work of Alfrey (7, 8) and of Sanders et al. (11) that acetate turnover has a half-life of 20 min or less, though Shepherd has reported that histone from CHO cells contains a stable internal acetylation site (17), and Byvoet has described turnover times ranging from 1 hour to 24 hours (18).

Many of the preceding studies utilized rather long pulses of $[^3H]acetate incorporation, which would tend to decrease the final yield of any modified forms that were turning over very rapidly. We have reinvestigated the incorporation and turnover of both acetylated and phosphorylated histones after very short pulses of radiolabel. We show that ~70% of the acetate incorporated in a 2-min pulse into histones $F_{sal}$, $F_6$, $F_{26}$ turns over with a half-life of ~3 min. It is possible to estimate that at any given time, approximately 30% of all of these histone molecules in the nucleus are modified in this way. We have also assayed for the dependence of acetylation and phosphorylation on active DNA synthesis.

MATERIALS AND METHODS

Labeling of HTC Cells with $[^3H]acetate and $[^32P]orthophosphate—HTC cells harvested in mid-log phase ($5 \times 10^6$ cells/ml) were pelleted by centrifugation at 300x g for 10 min and were then resuspended in fresh medium (Swim's S78) at half the previous volume $[^3H]acetate (25 mCi, 100 mCi/mmol, New England Nuclear)$ or $[^32P]orthophosphate (20 mCi, carrier-free, Amersham/Searle)$ was added and after the pulse period the incubation was cooled to 4$^\circ$ by diluting it 10-fold with ice-cold medium. After removal of the cells by centrifugation at 300x g for 10 min, the cell pellet was washed once in ice-cold medium and then resuspended in fresh medium at 3x and at normal cell densities ($5 \times 10^6$ cells/ml) for the chase period. Cells were har-
vested at desired times and frozen quickly in 95% ethanol-Dry Ice.

Preparation of Nuclei, Isolation and Analysis of Histone—Cells were homogenized in a solution containing 1% Triton, 0.25 M sucrose, 0.01 M MgCl₂, 0.01 M Tris, and 0.05 M NaHSO₃, pH 6.5 and the nuclei were pelleted by centrifugation at 1000 × g for 10 min. Nuclei were washed four times in the above medium, once in a solution containing 0.01 M Tris, 0.013 M EDTA, pH 8.0 and once in distilled water. The resulting chromatin gel was sheared in a Virtis '45' homogenizer for 1 min at 90 volts and brought to a final concentration of 0.4 N H₂SO₄. After stirring overnight at 4° the preparation was centrifuged at 27,000 × g for 20 min and the supernatant was dialyzed against 95% ethanol at 4°. The precipitated histone was collected, dried, and resuspended in 20%, sucrose, 0.9 M acetic acid, 0.5 M β-mercaptoethanol at approximately 1 mg/ml. Electrophoresis was performed on 25-cm gels by the procedure of Panyim and Chalkley (19) except that 15% acrylamide, 1.0 M urea were used. Gels were cut and digested in 0.4 ml of 30% H₂O₂ at 60° for 12 hours and counted in Bray's solution (20) using a Unilux III scintillation counter.

RESULTS

Biosynthesis and Turnover of Histone Acetate—The incorporation of [³H]acetate during a 10-min pulse and its subsequent turnover is shown in Fig. 1. It is apparent that substantial incorporation of acetate is observed even following such a short pulse. Major incorporation is found in the several levels of acetylation of F₁ and F₂. Both F₂a and F₂b show the presence of a lower but nonetheless significant degree of modification due to acetylation. The presence of acetate in the F₂b molecule was

![Figure 1](http://example.com/figure1.png)

Fig. 1. Incorporation and turnover of acetate after a short pulse. HTC cells were incubated with [³H]acetate for 10 min as described under “Materials and Methods.” After completion of the pulse the cells were cooled, the zero time sample taken, and the remaining cells washed and resuspended in fresh medium lacking [³H]acetate. Samples were then collected from the tissue culture system at the times indicated in the figure. Histones were isolated and analyzed electrophoretically as described under “Materials and Methods.” The associated counts are corrected to a constant unit area of input material onto each gel as judged by densitometer scans of the histone bands. Ac₁ and Ac₅ indicate modifications due to mono- and diacetylation.
not reported from sequence studies, though McCarty and his co-workers (11) had indicated previously that this histone fraction could undergo acetylation. It is known that the parental forms of Fzal, Fzaz, and F1 contain a NH2-terminal acetate group (1). Since this acetate group becomes rapidly associated with the molecule, and does not turnover (see below), it provides a measure of the extent of incorporation of acetate onto newly synthesized histone. The level of incorporation into the multi-acetylated forms of the histone molecules is greatly in excess of that on the NH2-terminus (Fig. 1) and thus it is apparent that much of the acetylation is occurring on histones other than those synthesized during the pulse period.

The turnover of the acetate groups is quite rapid, as about 75% of the radiolabel has been removed within 20 min. Subsequently almost all of the label other than that on the NH2 terminus of Fzal, Fzaz, and F1 has been removed within 4 hours after the pulse. Details of the turnover are shown graphically for F3 histone in Fig. 2 which indicates that at least two turnover rates are involved. Approximately 75% of the label has been removed within the first 20 min of the chase, indicating a $t_{1/2}$ ≤ 10 min. An additional 20% of the label turns over with $t_{1/2} = 30$ min. After 85 min, very little radiolabel remained associated with the acetylated forms of the F3 molecule.

The above experiment indicated that a substantial fraction of the acetate associated with F3 (and other histone fractions) turns over with a half-life ≤ 10 min. In order to more precisely define the nature of this turnover rate, we incubated HTC cells with [3H]acetate for 1 min and chased for appropriate time intervals. Typical data are shown in Fig. 3 again using F3 as an example. Each of the three levels of acetylation of F3 behave in a similar manner. These graphs contain two components. Approximately 60 to 70% of the radiolabel has a turnover time of $t_{1/2} = 3$ min and most of the remaining acetate groups have $t_{1/2} = 30$ min, in agreement with the previous experiments. A small fraction of acetate groups (5 to 8%) may have a lower rate of turnover. This graph provides evidence that the acetate chase is initiated quite promptly, and is clearly evidenced within 6 min of the chase period.

The combined data for all histones from studies analyzed in the manner of Figs. 2 and 3 are shown in Table I. Only

![Fig. 2. Turnover of [3H]acetate associated with F3. The radio-labeled acetate associated with all forms of modified F3 in Fig. 1 were added together and the level of [3H]acetate as a function of time is shown. The last point at 20 hours has been corrected for isotope dilution by new histone synthesis as the cells increased in number from 434,000 to 981,000 per ml.](image-url)

![Fig. 3. Turnover of [3H]acetate associated with various modified forms of F3 after a very short pulse. Histones were labeled with [3H]acetate during a 1-min exposure to HTC cells. The histones were isolated and subjected to electrophoresis as described under "Materials and Methods." Individual F3 sub-bands were cut out and counted. The counts per min are normalized to a constant area under the densitometer trace of the entire histone bands for each histone sample. The inset in the upper right hand corner is the corrected data from the rapid turnover obtained after correcting for the presence of the slower turnover rate.](image-url)
histone $F_{2a}$ does not provide clear evidence of a fraction which turns over more slowly than $t_{1/2} = 2$ to 3 min. All other histones (except $F_i$) contain both a fraction which turns over rapidly and also a somewhat less metabolically active component. The relative contents of these fractions vary somewhat. $F_{2a}$ contains the least amount of the more rapidly hydrolyzed fraction and the largest amount of the slower fraction.

It was not possible to assess whether there was a small fraction of the histone acetate which turned over with a half-life much in excess of 30 to 40 min because the values of the residual counts fell so rapidly towards baseline values following the exceedingly short pulses described above. Accordingly, we incubated HTC cells in the presence of [3H]acetate for a full cell generation time (17 hours), and followed the turnover of the various histone fractions during an extended chase period. The results of such an approach are shown in Fig. 4 in which we show the specific activity of the various fractions throughout a 16-hour chase period. The critical difference between this figure and Fig. 1 lies in the amount of [3H]acetate associated with the unmodified $F_{2a}$, $F_{2b}$, and $F_i$ molecules as a result of the substantial accumulation of acetate into the NH$_2$-terminal position of these molecules. Analysis of the specific activities of the various fractions throughout a 16-hour chase period indicates (a) that the NH$_2$-terminal acetate does not turnover significantly, and (b) the metabolically active acetate of all fractions (as opposed to the nonmetabolizable NH$_2$-terminal acetate) is totally removed within 3 hours of the chase period. We conclude that there is not a significant quantity of histone acetate with a turnover rate slower than that previously discussed. The distribution of [3H]acetate in $F_{2a}$, and its more slowly moving modified forms after long chase periods, closely parallels the distribution of mass between the parental and acetylated molecules, indicating that all classes of $F_{2a}$ are modified in the same way at the NH$_2$-terminus.

**Table I**

| Species of metabolically active histone acetate   | Amount | $t_{1/2}$ | Amount | $t_{1/2}$ |
|-------------------------------------------------|--------|----------|--------|----------|
| $F_3$                                           | 60-70% | 3        | 25%    | 30       |
| $F_{2b}$                                        | 75%    | 3        | 20%    | 40       |
| $F_{2a}$                                        | 50%    | 2-3      | 45%    | 40       |
| $F_{2a}$                                        | 80%    | 2-3      |        |          |

* Data computed from Fig. 3.
* Data computed from Figs. 2 and 3.

**Fig. 4.** Turnover of histone acetate after long term incorporation of radiolabel. The experimental design was the same as that in Fig. 3 except that the pulse was for a period of 17 hours. All counts are normalized to a constant amount of histone applied to the gel and corrected for isotope dilution due to increase in cell number during the chase period. $A_1$, $A_2$, and $A_3$ indicate modifications due to mono- and diacetylation.
Fig. 5. Effect on acetylation of inhibition of DNA and histone synthesis. Histones were labeled for 10 min with \(^{3}H\)acetate either in the presence (+CH) or absence (−CH) of cycloheximide. The cells were collected and histone analyzed for associated \(^{3}H\)acetate as described above. Prior to labeling with \(^{3}H\)acetate, the cycloheximide-treated cells were preincubated 45 min in medium containing cycloheximide (10 \(\mu g/ml\)). Ac\(_{1}\), Ac\(_{2}\), and Ac\(_{3}\) indicate modifications due to mono-, di-, and triacetylation.

Fig. 6. Incorporation and turnover of phosphate after a short pulse. HTC cells were incubated with \(^{32}P\) orthophosphate for 10 min, chased, and analyzed as described in the legend to Fig. 1. P\(_{1}\) and P\(_{2}\) indicate modifications due to mono- and di-phosphorylation.
in this paper, as high levels of incorporation were possible and we could analyze for low level acquisition of phosphate groups. Furthermore, using a short pulse, we could analyze for turnover rates of such rapidity that they might not have been observed previously. The value of this approach is documented in Fig. 6 in which we see the results of a 10-min pulse of \(^{32}P\) followed by a chase period extended for 20 hours. The incorporation of \(^{32}P\) after a 10-min pulse is in many ways quite different from what we and several other groups have observed using longer pulse periods. In this experiment the most extensively labeled fraction is \(F_{2a2}\). The second highest labeled fraction is \(F_1\) followed by \(F_3\) and finally at a very low level by \(F_{2a1}\). Histone \(F_{2b}\) is not phosphorylated. If \(F_{2b}\) is isolated by the method of Johns (22), a vast quantity of \(^{32}P\) is present in this fraction; however, electrophoresis removes the label in its entirety from the \(F_{2b}\) histone which migrates free from radioactivity. In addition, the high resolution gels (Fig. 6) leave no doubt that \(F_{2a2}\) and not \(F_{2b}\) is the recipient of the phosphate groups. The turnover of the various histone phosphate fractions can be compiled from the data of Fig. 6 and is shown in Fig. 7. The reason that \(F_{2a2}\) shows a greater accumulation of label than \(F_1\) in short pulse experiments but not in longer pulses now becomes clear, inasmuch as \(F_{2a2}\) contains a fraction with a much more rapid turnover than that seen for \(F_1\). Approximately 60% of \(F_{2a2}\) phosphate turns over with a \(t_{1/2} = 40\) min. The \(F_1\) phosphorylated in the short pulse turns over with a \(t_{1/2} = 3\) hours which is significantly different from the long term \(t_{1/2}\) which has a value of 5 hours in these cells (23). Both \(F_3\) and \(F_{2a1}\), like \(F_{2a2}\), have two turnover rates for their phosphate modifications; a faster rate of hydrolysis with \(t_{1/2} = 30\) min and a slower with \(t_{1/2} = 2\) to 3 hours. The initiation of the chase period is much slower for \([\text{\textsuperscript{32}}P]\)- than for \([\text{\textsuperscript{3}}H]\)acetate, presumably reflecting a greater time needed for depletion of the phosphate pool.

Effect of Inhibition of DNA and Protein Synthesis on Histone Phosphorylation—A comparison of the incorporation of \(^{32}P\) into the various histone fractions, in growing cells and cells in which DNA and protein synthesis was inhibited, is shown in Fig. 8. Histone \(F_1\) shows a 50% decrease in phosphate incorporation in agreement with previous observations (21), histone \(F_{2a2}\) shows a small (15%) decrease, whereas histone \(F_3\) is apparently unaffected by this block in macromolecular synthesis. Although the level of incorporation of \(^{32}P\) into \(F_{2a2}\) is low in the control cells, it appears that it is reduced by cycloheximide treatment. The effect of cycloheximide treatment on the turnover of the various phosphorylated histone molecules was also studied in a manner analogous to the studies with acetylated histones. Unfortunately

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**Fig. 7.** Turnover of \(^{32}P\)phosphate associated with histones. The total radiolabeled phosphate associated with the various modified species of each of \(F_2\), \(F_{2a1}\), \(F_{2a2}\), and \(F_1\) is shown as a function of time (min). Data are from the results of Fig. 6.
the termination of the $^{32}$P pulse period is much slower if cycloheximide was present during the pulse period and these studies were not pursued further.

**Discussion**

The capacity for studying acetylation and phosphorylation of histones after very short pulses of radiolabel has been developed. The termination of a pulse of PHacacetate occurs promptly and the chase period can be initiated with some precision. This is not the case for phosphate incorporation and at least 40 min must elapse from the completion of the pulse period before the true chase begins and effective turnover values can be estimated.

All histone fractions are acetylated. Fractions $F_{2a1}$, $F_{2a2}$, and $F_1$ are $NH_2$-terminally acetylated (1) and this is a stable modification, which does not turn over significantly in a full cell cycle. Histones $F_{2a1}$, $F_{2a2}$, $F_{2b}$, and $F_1$ are all acetylated internally in a form which is metabolically highly active. This is in agreement with the observations of McCarthy and his colleagues in the dog erythrocyte system (11). After a short 1-min pulse, about 70% of the associated acetate turns over with a $t_{1/2}$ = 3 min. This is a much shorter half-life than any value previously reported. However, analysis of earlier data (7, 8, 11) indicates that a significant fraction of histone acetate was turning over with a $t_{1/2}$ of <20 min. A smaller fraction of the acetate incorporated into HTC histone molecules turns over with a $t_{1/2}$ = 30 to 40 min.

The incorporation of labeled acetate into the $NH_2$-terminal position of $F_{2a1}$ provides us with a means for estimating the extent of acetylation of the entire population of $F_{2a1}$ molecules during a short pulse period. Thus, if after a 10-min pulse of PHacacetate we find "p" counts per min associated with the $NH_2$-terminal acetylated form of a molecule and "y" and "z" counts per min associated with internally mono- and diacetylated forms of the molecule, then the fraction of the total $F_{2a1}$ molecules which are internally acetylated is \( [(y - p) + (\frac{1}{2}(z - p))] / p \times 100 \% \) (there are 96 units of 10 min in the 16-hour cell cycle of HTC cells). Using the data of Fig. 1 we find that 25 to 30% of all the $F_{2a1}$ molecules in the cell have been acetylated during the 10-min period. Obviously old histones must be extensively acetylated, though of course this does not at all exclude the possibility that newly synthesized histone is also acetylated. Previously, although Dixon had estimated that newly synthesized $F_{2a1}$ was acetylated at the time of its deposition (15), no means had existed to obtain estimates of the extent of acetylation of both new and old histone such as those deduced above.

Inhibition of DNA and histone synthesis leads to a small but significant decrease in acetylation of the more extensively modified forms of $F_{2a1}$. This is consistent with the observations by Dixon that this histone fraction is extensively acetylated shortly after its synthesis (15). We have recently confirmed this observation in HTC cells. Thus it is reasonable to expect a decrease in over-all acetylation of $F_{2a1}$ upon inhibition of histone synthesis with cycloheximide. However, the acetylation of the other fractions does not respond in a similar manner, and thus the acetylation of new $F_{2a1}$ may be serving a different function to that of the acetylation of other histone fractions.

After short pulses of $^{32}$P, histone $F_{2a2}$ is labeled more extensively than $F_1$, an observation in contrast to all previous reports. However, analysis of histone phosphate turnover explains the apparent discrepancy (23-25). $F_{2a2}$ has a substantial amount of a phosphate fraction which is turning over about 4 to 5 times faster than $F_1$ phosphate. Thus, even though $F_1$ is phosphorylated somewhat more slowly than $F_{2a2}$ (and thus shows a lower degree of $^{32}P$ labeling in short pulses), after an extended pulse period, $F_1$ accumulates a greater amount of $^{32}P$ than $F_{2a2}$ because of its much lower rate of phosphate removal.

The effect of inhibiting DNA and histone synthesis upon histone phosphorylation in general produces a moderate decrease in $^{32}P$ incorporation. $F_1$ is most affected and $F_{2a1}$ and $F_2$ the least. The decrease in phosphorylation of $F_1$ is due to inhibition of the more rapid phosphorylation of newly synthesized $F_1$, whereas old $F_1$ continues to be phosphorylated at a slower rate (26). It is not known whether this is true for the other three histone fractions which are phosphorylated. Phosphorylation of $F_3$ appears to be associated with a mitotic event (24), and it is perhaps not surprising that it is not dependent upon histone synthesis and is therefore but little affected by cycloheximide addition.

Several hypotheses have been presented concerning the biologic functions of histone modifications. These include (a) gene activation through acetylation (8, 27) or phosphorylation (28); (b) histone deposition through the combined action of acetylation and phosphorylation (12); and (c) chromosome condensation due to phosphorylation (24, 29). To some extent the observations reported in this paper are consistent with proposal b, but it is clear that the acetylation is much too extensive and occurs to such a degree on old histone as to render this only a part of their total function. Furthermore acetylation has been reported in non-dividing cells (11). The extent of the acetylation also appears to exclude a specific gene activating event, even though it could be working indirectly to facilitate RNA biosynthesis. However, it seems that the entire chromosome is probably exposed to this type of modification, as both euchromatin and heterochromatin are acetylated to the same degree (30). We envisage a 2-fold function for acetylation. On the one hand it may play a role in the deposition of specific histone fractions (mostly $F_{2a1}$) as suggested by Dixon (12), and on the other hand it may serve to temporarily break a critical interaction to permit an additional function to be performed. For instance, it is conceivable that a structural role might depend upon a key electrostatic interaction and yet RNA polymerase movement along the chromosome might require the electrostatic bond be temporarily and briefly broken. Why the cell should elect to acetylate so extensively rather than at a few specific regions to be transcribed might simply reflect the high energy expenditure required for high precision acetylation.

Phosphorylation and acetylation were first invoked to explain the electrophoretic microheterogeneity of histones in 1968 (19). It is now clear that the levels of such modified forms of histone detected in the polyacrylamide gels are the result of a vigorous subsequent hydrolysis.

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