References and Notes

1. D. Branton, *Proc. Natl. Acad. Sci. U.S.A.* **55**, 1048 (1966); P. Pinto da Silva and D. Branton, *J. Cell Biol.* **45**, 598 (1970); T. W. Tillach and V. T. Marchesi, *ibid.*, p. 649.
2. K. A. Fisher, *Science* **190**, 983 (1975); *Proc. Natl. Acad. Sci. U.S.A.* **73**, 173 (1976).
3. J. Yu and D. Branton, *Proc. Natl. Acad. Sci. U.S.A.* **73**, 3891 (1976); J. P. Segrest, T. Gulik-Krzywichi, C. Sardet, *ibid.* **71**, 3294 (1974).
4. P. Pinto da Silva and G. L. Nicolson, *Biochim. Biophys. Acta* **363**, 311 (1974).
5. T. J. Mueller and M. Morrison, *J. Biol. Chem.* **249**, 7568 (1974).
6. T. J. Mueller, A. W. Dow, M. Morrison, *Biochem. Biophys. Res. Commun.* **72**, 94 (1976).
7. O. O. Blumenfeld, P. M. Gallop, T. H. Liao, *ibid.* **48**, 242 (1972); C. G. Gahmberg and L. C. Andersson, *J. Biol. Chem.* **252**, 5888 (1977).
8. C. Pricam, K. A. Fisher, D. S. Friend, *Anat. Rec.* **189**, 595 (1977).
9. L. H. Engstrom, thesis, University of California, Berkeley (1970).
10. T. L. Steck, *J. Cell Biol.* **62**, 1 (1974).
11. M. S. Bretscher, *J. Mol. Biol.* **58**, 775 (1971); D. R. Phillips and M. Morrison, *FEBS Lett.* **18**, 95 (1971).
12. G. Fairbanks, T. L. Steck, D. F. H. Wallach, *Biochemistry* **10**, 2606 (1971).
13. J. K. Tuech and M. Morrison, *Biochem. Biophys. Res. Commun.* **59**, 352 (1974); M. Silverberg, H. Furthmayr, V. T. Marchesi, *Biochemistry* **15**, 1448 (1976).
14. D. Kobylka *et al.*, *Arch. Biochem. Biophys.* **148**, 475 (1972).
15. E. Beutler, C. West, K. G. Blume, *J. Lab. Clin. Med.* **88**, 328 (1976).
16. R. Arnon, *Methods Enzymol.* **19**, 226 (1970); T. Nakai, P. S. Otto, T. F. Whayne, *Biochim. Biophys. Acta* **422**, 280 (1976).
17. J. R. Pringle, *Methods Cell Biol.* **12**, 149 (1975).
18. T. Bachi, K. Whiting, M. J. A. Tanner, M. N. Metaxas, D. J. Anstee, *Biochim. Biophys. Acta* **464**, 635 (1977); J. M. Wolosin, H. Ginsberg, Z. I. Cabantchik, *J. Biol. Chem.* **252**, 2419 (1977).
19. T. W. Tillack, R. E. Scott, V. T. Marchesi, *J. Exp. Med.* **135**, 1209 (1972); G. L. Nicolson, *J. Cell Biol.* **57**, 373 (1973); C. W. M. Grant and H. M. McConnell, *Proc. Natl. Acad. Sci. U.S.A.* **71**, 4653 (1974); T. J. Triche, T. W. Tillack, S. Kornfeld, *Biochim. Biophys. Acta* **394**, 540 (1975).
20. A. Elgsaeter, D. M. Shotton, D. Branton, *Biochim. Biophys. Acta* **426**, 101 (1976); S. C. Liu, G. Fairbanks, J. Palek, *Biochemistry* **16**, 4066 (1977).
21. G. L. Nicolson and R. G. Painter, *J. Cell Biol.* **59**, 395 (1973).
22. U. K. Laemmli, *Nature (London)* **227**, 680 (1970).
23. W. M. Bonner and R. A. Laskey, *Eur. J. Biochem.* **46**, 83 (1974).

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Amino Acid Sequence Homology Between Histone H5 and Murine Leukemia Virus Phosphoprotein p12

Abstract. *The amino terminal acid sequences of several mouse leukemia virus phosphoproteins (p12) show definite homology with the amino terminal conserved region of H5 histones, the phosphorylated nuclear proteins of nucleated erythrocytes. Differences in the amino acid compositions of the two groups of proteins seem to rule out the possibility that they evolved from a single common ancestral gene. The finding of sequence homology between viral p12's and cellular histones, however, is consistent with evolution of retrovirus structural proteins by a process of differentiation from preexisting cellular genes. The conserved primary and secondary structure at the amino terminal region, common to both groups of proteins, may be related to their common function of nucleic acid binding modulated by phosphorylation.*

Histone H5 is a phosphorylated nuclear protein found only in nucleated erythrocytes (*1*). Partial primary structure studies of several H5 proteins isolated from different avian sources indicate extensive amino acid sequence homology (*1-3*). In addition, H5 histones show definite homology with H1 histones isolated from a wide variety of sources (*4*). During erythropoiesis, H1 is replaced by H5 in the nucleus of the developing nucleated erythrocyte (*5*). Through the early stages of erythropoiesis, H5 is highly phosphorylated and becomes dephosphorylated as the erythrocyte matures. Dephosphorylation of H5 appears to coincide with chromatin condensation and genomic inactivation (*6, 7*). Although the precise function of H5 is unknown, it is probably involved in genomic regulation and may serve to maintain a highly repressed state of avian erythrocyte chromatin (*1, 7*).

Type C leukemia viruses contain a phosphoprotein (p19 in avian, p12 in murine, and p15 in viruses of primate origin) which has been shown to bind specifically to homologous viral RNA (*8-10*). A low level of phosphorylation is necessary for binding activity, but highly phosphorylated forms of the proteins do not bind to RNA (*10*). It has been postulated that these phosphoproteins may have a role in viral assembly and in regulation of transcription (*9-11*). Partial amino acid sequences have been determined for several p12 proteins isolated from murine viruses (*12, 13*). We now report that the amino acid sequences of conserved regions near the amino terminus of the leukemia virus p12 proteins show a distinct homologous relation to conserved regions near the amino terminus of the H5 histones.

In Table 1, the amino terminal amino acid sequences of H5 histones isolated from goose (*3*) and chicken (*2*), together with the amino terminal sequences of various leukemia virus p12 proteins (*12, 13*), are aligned to give a maximum number of identities. Chicken H5 is aligned with goose H5 by introducing a gap between residues 10 and 11 in the chicken sequence (*3*) (position 8 in the alignment, Table 1). The AKR mouse leukemia virus (MuLV) p12 sequence is aligned with the other p12 sequences by placing a gap in positions 8 and 9 in the AKR sequence (*12*). The H5 and p12 sequence regions of primary interest are residues 4 to 15 in the goose H5 and 1 to 12 in Moloney (Mo)-MuLV p12 (positions 1 to 12 in the alignment). These two sequences give six identities out of 12 residues without the introduction of a gap in either sequence. The introduction of a gap at position 13 in the alignment of the H5 sequences increases the number of positionally identical amino acids between

Table 1. Alignment of amino terminal amino acid sequences of type C leukemia virus p12 proteins to avian histone H5 proteins. Rauscher murine leukemia virus (R-MuLV), AKR murine leukemia virus (AKR-MuLV), and Moloney murine leukemia virus (Mo-MuLV) p12 sequences are aligned with goose and chicken histone H5 sequences with the introduction of gaps (- * -). Residues in italics are positionally identical when comparing at least one of the H5 histones to one of the p12's; residues in bold face are considered to be functionally homologous in the two groups of proteins. In the chicken H5, there are at least two allelic genes for chicken H5, giving either Arg or Gln at residue 15 (*24*), position 14 in the alignment (last line of the table).

Source	Protein	Reference	Sequence														
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
R-MuLV	p12	(*12*)	*Pro*	**-Thr**	*-Leu*	**-Thr**	-Ser	-Pro	-Leu	-Asn	**-Thr**	*-Lys*	*-Pro*	**-Arg**	-Pro	*-Gln*	*-Val*
AKR-MuLV	p12	(*12*)	*Pro*	-Ala	*-Leu*	**-Thr**	*-Pro*	**-Ser**	-Leu	- *	- *	*-Lys*	*-Pro*	**-Arg**	-Pro	-Ser	**-Leu**
Mo-MuLV	p12	(*13*)	*Pro*	-Ala	*-Leu*	**-Thr**	*-Pro*	**-Ser**	-Leu	**-Gly**	*-Ala*	*-Lys*	*-Pro*	*-Lys*	-Pro	*-Gln*	*-Val*
Goose	H5	(*4*)	Thr-Asp-Ser	*-Pro*	-Ile	-Pro	**-Ala**	*-Pro*	**-Ala**	-Pro	**-Ala**	*-Ala*	*-Lys*	*-Pro*	*-Lys*	- *	**-Arg**	-Ala
Chicken	H5	(*4*)	Thr-Glu-Ser	-Leu	**-Val**	*-Leu*	**-Ser**	*-Pro*	**-Ala**	-Pro	- *	*-Ala*	*-Lys*	*-Pro*	*-Lys*	- *	*-Gln*	*-Val*

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the p12's and the H5 histones: glutamine in position 14 and valine in position 15.

Table 2 gives the amino acid compositions of Mo-MuLV p12 and goose H5, which represent their respective protein classes. From these data the probability of finding a given number of identities when comparing a given number of residues can be calculated according to the procedure of Haber and Koshland (*14*). This procedure is based upon the logical assumption that the mole fraction of a given residue in a protein gives the probability of finding that residue at any given locus in the sequence. In the case of the comparison of Mo-MuLV p12 and goose H5, the probability of finding six identities in any sequence of 12 residues is 1×10^{-4}. Since the mole fraction of lysine is high in the H5 histones, the probability of finding a lysine at a given position is correspondingly high. However, only a relatively small fraction (one-fourth) of the total lysine residues is found in the amino terminal half of the molecule (*4*). When the amino acid composition of the amino terminal 100 residues of goose H5 is used, the probability of finding 6 out of 12 identities with Mo-MuLV p12 is even less (6×10^{-5}). One of the most striking features of the sequence homology shown in Table 1 is that all the lysines of Mo-MuLV p12 (2/2) are involved in giving identities in the alignment with H5 histones. When this is taken into account, the probability of finding such an alignment is further reduced. Thus, it is unlikely that the sequence homology is the result of chance.

In addition to the positional identities, functionally homologous (*14*) amino acid residues appear in position 2 (Val-Ile, Val-Thr, Ala-Thr) (*15*), position 4 (Ser-Ala-Thr), position 8 (Ala-Gly), position 9 (Ala-Thr), position 12 (Lys-Arg), position 14 (Gln-Arg), and position 15 (Val-Leu). Thus, if we consider all the identities and homologies that occur in the compared region extended through position 15 in Table 1, we obtain the total number of correspondences (identities plus homologies) for any two sequences. In the aligned region the degree of relatedness (total number of correspondences) of Mo-MuLV p12 to goose or chicken H5 is as high as or higher than that of chicken H5 to goose H5 or that of AKR-MuLV p12 to Rauscher (R)-MuLV p12 (Table 3).

The Lys-Pro-Lys/Arg sequence at positions 10 to 12 in Table 1 is conserved in all known viral p12 proteins and H5 histones. The frequency of occurrence of this sequence in other known proteins was determined for the 472 complete or partial structures listed by Dayhoff *et al.* (*16*). The Lys-Pro-Lys sequence was found in nine listed structures; the Lys-Pro-Arg sequence was found in four listed structures. All but three (see below) of these structures showed little or no additional correspondence to either the H5 histones or the viral p12 proteins. The sequence Thr-Lys-Pro-Arg found at residues 9 through 12 in R-MuLV p12 is also found in human immunoglobulin gamma 4 (Vin), and in human immunoglobulin gamma 1 (Eu). In both immunoglobulin gamma chains, this sequence is not located near the amino terminus and shows little or no additional amino acid sequence correspondence to either H5 histones or viral p12 proteins. The sequence Lys-Pro-Lys-Gln found in chicken H5 histone at residues 12 to 15 was also found at residues 13 to 16 in the mu heavy chain of human immunoglobulin OU (MHHUOU). These two amino terminal amino acid sequences could be aligned to give eight identities out of the first 16 residues with the introduction of a single gap in the chicken H5 histone sequence. Alignment of the Mo-MuLV p12 amino terminal 12 residues with the same segment of the MHHUOU sequence required the introduction of one gap in each sequence to produce five identities. On the basis of an analysis according to the method of Haber and Koshland (*14*), this comparison would suggest a possible structural relation between the amino terminal ends of chicken H5, MHHUOU, and Mo-MuLV p12. Further analysis suggests that the apparent relation of the immunoglobulin chains to the other two proteins may be spurious. Chou and Fasman (*17*) have established a set of generalized rules for predicting secondary structure from amino acid sequences. When these methods are applied, the amino terminal sequence of the viral p12 proteins and H5 histones are predicted to be coiled structures, whereas the first five or more residues of MHHUOU are predicted to be involved in β structure, and residues 8 through 15 are predicted to be part of the coiled structure followed by another region of β structure. These predictions are in agreement with x-ray crystallographic data on immunoglobulins (*18*) where residues 10 through 15 are involved in a bend between β structures. The amino terminal amino acid sequence of MHHUOU shows considerable homology with several different immunoglobulin gamma chains (*19*) and mu chains (*20*), but of the Lys-Pro-Lys-Gln sequence representing residues 13 to 16, only the proline is conserved. Evidently this segment of the immunoglobulins is involved in a bend between β structures where considerable variation can be allowed in the residues on either side of the necessary proline residue. Thus, it appears that the apparent amino acid sequence similarities between the immunoglobulin and the phosphoproteins may be the result of chance and the method of comparison. Conversely, the H5 histones and the viral p12 proteins appear to be under selective pressure to conserve the highly related

Table 2. Amino acid compositions (residues per mole with mole percent in parentheses) of Mo-MuLV p12, goose H5 histone, and the amino terminal 100 residues of goose H5 histone.

Amino acid residue	Mo-MuLV p12*	Goose H5 histone†	*N*-terminal 100 residues of goose H5 histone
Lys	2 (1.9)	49 (24.8)	11 (11)
His	0 (0)	3 (1.5)	3 (3)
Arg	7 (6.5)	22 (11.2)	9 (9)
Asp	11 (10.3)	4 (2.0)	4 (4)
Thr	5 (4.7)	8 (4.1)	5 (5)
Ser	8 (7.5)	21 (10.7)	10 (10)
Gly	7 (6.5)	6 (3.0)	6 (6)
Pro	28 (26.2)	19 (9.6)	8 (8)
Gly	8 (7.5)	10 (5.0)	8 (8)
Ala	8 (7.5)	33 (16.8)	5 (5)
Val	2 (1.9)	5 (2.5)	4 (4)
Met	1 (0.9)	1 (0.5)	1 (1)
Ile	1 (0.9)	6 (3.0)	6 (6)
Leu	17 (15.9)	7 (3.5)	6 (6)
Tyr	1 (0.9)	3 (1.5)	3 (3)
Phe	1 (0.9)	1 (0.5)	1 (1)

*Samples were hydrolyzed in 6*N* HCl at 110°C and analyzed on a Beckman 121M amino analyzer as described (*12*). †Data taken from Yaguchi *et al.* (*4*).

Table 3. Number of correspondences between sequences shown in Table 1. The figures represent the number of all corresponding residues between the compared regions of any two sequences shown in Table 1. Two residues correspond when they are identical or functionally homologous (*14*).

Item	Chicken H5	Goose H5	Mo-MuLV p12	R-MuLV p12	AKR-MuLV p12
Chicken H5	15	9	10	9	8
Goose H5		15	10	8	7
Mo-MuLV p12			15	12	12
R-MuLV p12				15	10
AKR-MuLV p12					15

Lys-Pro-Lys/Arg sequences in a coiled structure near the amino acid terminal regions.

The amino acid compositions of the two groups of phosphoproteins are obviously different. This seems to rule out the possibility that the two groups evolved from a common ancestor. However, there remains the possibility that viral p12 evolved from H5 histones or related proteins through a genetic recombination process involving only the amino terminal end of the H5 histones. Alternatively, the sequence homology may be the result of convergent evolution. The finding of sequence homology between viral and cellular structural proteins is consistent with the emergence of infectious entities by a process of differentiation from preexisting cellular genes. Vestiges of these primordial origins might be more readily detected in retroviruses because of their inheritance in the cellular genome. Given recent information on messenger RNA splicing (*21*) and shifts in physical location of specific DNA segments during maturation of the immune system (*22*), it is not unreasonable to suggest that similar mechanisms might have contributed to the origin of viral structural proteins. Thus, several cellular genes of diverse function could have contributed to the origin of individual virion polypeptides. This speculation is readily derived from the protovirus hypothesis of Temin (*23*), in that the coding sequences assume their appropriate physical alignments by a series of rearrangements mediated by cellular reverse transcriptase. Further analyses of complete sequences of retrovirus polypeptides will be necessary to fully evaluate our speculations; however, this could provide a rigorous evaluation of current theories of retrovirus origin.

The sequence homologies between H5 histones and the viral p12 proteins indicate a conserved structural feature common to both groups of proteins and, in turn, a common function. As we pointed out above, both the H5 histones and the viral p12 proteins bind to nucleic acids through an interaction modulated by phosphorylation of the proteins. It has been suggested that the amino terminal portion of chicken H5 may participate in this binding (*7*). The amino terminal sequence homology between viral p12 proteins and H5 histones could suggest that the amino terminal regions of p12's also may be involved in nucleic acid binding or phosphorylation (or both).

Further studies may determine whether or not the common structure-function relationship implied here between proteins involved in erythroid differentiation and proteins isolated from leukemia viruses could be related to molecular mechanisms of viral leukemogenesis.

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References and Notes

1. L. S. Hnilica, in *The Structure and Biological Function of Histones*, L. S. Hnilica, Ed. (CRC Press, Cleveland, Ohio, 1972), p. 30
2. P. J. Greenway, *Biochem. J.* **124**, 319 (1971); A. Garel, A. Mazen, M. Champagne, P. Sautiere, D. Kmiecik, O. Loy, G. Biserte, *FEBS Lett.* **50**, 195 (1975); P. Sautiere, G. Briand, D. Kmiecik, O. Loy, G. Biserte, A. Garel, M. Champagne, *ibid.* **63**, 164 (1976).
3. V. Seligy, C. Roy, M. Dove, M. Yaguchi, *Biochem. Biophys. Res. Commun.* **71**, 196 (1976).
4. M. Yaguchi, C. Roy, M. Dove, V. Seligy, *ibid.* **76**, 100 (1977).
5. C. Dick and E. W. Johns, *Biochem. Biophys. Acta* **175**, 414 (1969); A. Mazen and M. Champagne, *Biochimie* **54**, 1273 (1972).
6. M. T. Sung, *Biochemistry* **16**, 286 (1977).
7. ——— and E. F. Freedlender, *ibid.* **17**, 1884 (1978).
8. R. V. Gilden, in *Molecular Biology of Animal Viruses*, D. P. Nayak, Ed. (Dekker, New York, 1977), vol. 1, pp. 435–542.
9. B. K. Pal and P. Roy-Burman, *J. Virol.* **15**, 540 (1975); B. K. Pal, R. M. McAllister, M. B. Gardner, P. Roy-Burman, *ibid.* **16**, 123 (1975); A. Sen and G. J. Todaro, *Science* **193**, 326 (1976); A. Sen, C. J. Sherr, G. J. Todaro, *Cell* **7**, 21 (1976); A. Sen and G. J. Todaro, *ibid.* **10**, 91 (1977).
10. A. Sen, G. J. Sherr, G. J. Todaro, *Cell* **10**, 489 (1977).
11. E. Erikson, J. S. Brugge, R. L. Erikson, *Virology* **80**, 177 (1977).
12. S. Oroszlan, L. E. Henderson, T. D. Copeland, C. W. Long, J. N. Ihle, R. V. Gilden, *Proc. Natl. Acad. Sci. U.S.A.* **75**, 1404 (1978).
13. S. Oroszlan, L. E. Henderson, T. D. Copeland, unpublished data.
14. J. E. Haber and D. E. Koshland, Jr., *J. Mol. Biol.* **50**, 617 (1970).
15. Abbreviations for amino acid residues are Ala, alanine; Arg, arginine; Asn, asparagine; Asp, aspartic acid; Cys, cysteine; Gln, glutamine; Glu, glutamic acid; Gly, glycine; His, histidine; Ile, isoleucine; Leu, leucine; Lys, lysine; Met, methionine; Phe, phenylalanine; Pro, proline; Ser, serine; Thr, threonine, Trp, tryptophan; Tyr, tyrosine; and Val, valine.
16. M. O. Dayhoff, C. M. Park, L. T. Hunt, W. C. Barker, P. J. McLaughlin, *Protein Segment Dictionary 72* (National Biomedical Research Foundation, Washington, D.C., 1972).
17. P. Y. Chou and G. D. Fasman, *Biochemistry* **13**, 222 (1974).
18. R. J. Poljak, L. M. Amzel, H. P. Avey, B. L. Chen, R. P. Phizackerley, F. Saul, *Proc. Natl. Acad. Sci. U.S.A.* **70**, 3305 (1973); D. M. Segal, E. A. Padlan, G. H. Cohen, S. Rudikoff, M. Potter, D. R. Davis, *ibid.* **71**, 4298 (1974).
19. F. W. Putnam, A. Shimizu, C. Paul, T. Shinoda, *Fed. Proc. Fed. Am. Soc. Exp. Biol.* **31**, 193 (1972); M. Wikler, H. Köhler, T. Shinoda, F. W. Putnam, *Science* **163**, 75 (1969).
20. J. D. Capra and J. E. Hopper, *Immunochemistry* **13**, 995 (1976).
21. S. M. Berget, C. Moore, P. A. Sharp, *Proc. Natl. Acad. Sci. U.S.A.* **74**, 3171 (1977).
22. S. Tonegawa, N. Hozumi, C. Brack, R. Schuller, in *ICN-UCLA Symposia on Molecular and Cellular Biology* vol. 6, *Immune System: Genetics and Regulation*, E. E. Sercarz, L. A. Herzenberg, C. F. Fox, Eds. (Academic Press, New York, 1977), p. 43.
23. H. M. Temin, *Science 192*, 1075 (1976).
24. P. J. Greenway and K. Murray, *Nature (London) New Biol.* **229**, 233 (1971).
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Control of Oscillations in Hematopoiesis

Abstract. *Results of a mathematical analysis of models of hematopoietic systems introduced by Mackey and Glass are given. The models include a constant time lag, and it is shown that this lag has a critical value above which oscillations in blood cell concentration occur. To reduce the likelihood of disease associated with such oscillations, physiologists should seek to learn how to increase this critical value of the lag.*

Mackey and Glass (*1*) introduced mathematical models for blood cell production with a constant lag $\tau > 0$ between cell genesis in the bone marrow and release into the bloodstream. Their models have the form

$$\frac{dx(t)}{dt} = \Lambda(x(t - \tau)) - ax(t) \qquad (1)$$

where $x(t)$ is the cell density at time t, a is a constant death rate, and Λ is a smooth function describing the generation of cells of a particular kind, such as erythrocytes. We report the results of a mathematical analysis of these models, which leads to qualitative advice to the physiologist.

This analysis, which is essentially nonlinear, reveals that there exists a critical value of the lag, τ_c. For values of τ in an interval on one side of τ_c, the cell density exhibits stable oscillations with amplitude which increases linearly with $|\tau - \tau_c|^{1/2}$. For the nonlinear terms in Λ used in (*1*) (see Eq. 2 below) these oscillations, which are symptomatic of hematopoietic disease, occur for $\tau > \tau_c$. Thus our qualitative advice is to seek to affect the system so as to increase τ_c and, thereby, possibly suppress oscillatory behavior of the cell density.

To illustrate, consider the particular choice of the function introduced in (*1*) [see also (*2*)], namely

$$\Lambda(x(t - \tau)) = \frac{\beta_0 \theta^n x(t - \tau)}{\theta^n + x^n(t - \tau)} \qquad (2)$$

This corresponds to production being a single-humped function of the delayed density; for physiological details and ref-

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