afference to cortex in each zone. Our results are consistent with this interpretation, and we also suggest that cells are assigned to laminae as they arrive and from inside to out (*6, 13*) in direct proportion to the amount of afference, with any mismatch between the amount of cells generated and availability of afference (or efference) absorbed by cell death in the last generated, outside lamina.

Evidence from the reeler mutant mouse suggests that the connectivity and identity of cortical neurons is independent of laminar position (*14*), a finding that appears to be in conflict with our observations in the hamster. However, in reeler, cortical cells still occupy the same position relative to each other and are still stratified by birthday; only their position relative to the ventricular zone and the marginal zone is altered. It is possible that only the order of termination is altered and not the mechanism of cellular specification. In the reeler, we would thus predict that the last generated, inside lamina should show the most variability in cell loss.

Whether cell death plays a role in the organization of other cortical areas in other species as well as what controls a cortical cell's viability are not yet known. Studies of the loss of callosal and subcortical cortical projections in early development suggest that cell death is not involved in the error correction function of axon retraction (*15*). Rather, cell death appears to be a clue to the mechanism of specification of a cortical neuron's identity.

BARBARA L. FINLAY
MICHAEL SLATTERY
Department of Psychology,
Cornell University,
Ithaca, New York 14853

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Deficiency of a Kidney Metalloproteinase Activity in Inbred Mouse Strains

Abstract. *Kidneys from BALB/c mice contain a potent metalloendoproteinase, termed meprin, that is active against large proteins as well as small peptides. The enzyme is present in mouse strains C57BR/cdJ, C57BL/6J, BALB/cJ, A/J, DBA/1J, CD/1, Swiss, and ICR. Three related inbred strains, CBA/J, CBA/CaJ, and C3H/He, are markedly deficient in this enzymatic activity. This is the first report of a heritable deficiency of an intracellular proteinase in mammalian tissues. Meprin deficiency appears to have arisen as an early event in the development of the C stock. Furthermore, meprin is present in the progeny of a cross between a meprin-sufficient female (C57BL/6) and a meprin-deficient male (C3H/HeN), an indication that the trait for the deficiency is recessive.*

The study of heritable enzyme deficiencies in animals has contributed to our understanding of metabolic processes, and many specific deficiencies have been identified (*1*). Although many inherited hydrolase (E.C. 3.x.x.x) deficiencies have been reported, only a few inborn errors of metabolism involve one subdivision of this group, the proteinases (subclass peptidyl-peptide hydrolases, E.C. 3.4.x.x). Furthermore, the known inherited deficiencies in proteinases are limited to extracellular enzymes such as the complement component C_3 and a collagen-processing peptidase (*2*). As far as we know, no inherited deficiency of an integral cellular proteinase has yet been documented. We present here data demonstrating such a deficiency.

Meprin (metalloendopeptidase from renal tissue) was first discovered and purified from kidneys of the BALB/c mouse (*3*). It is a membrane-bound endopeptidase that degrades a wide range of substrates including large proteins. It is active optimally at alkaline *p*H values and is inhibited by compounds that typically inhibit metalloenzymes (EDTA,

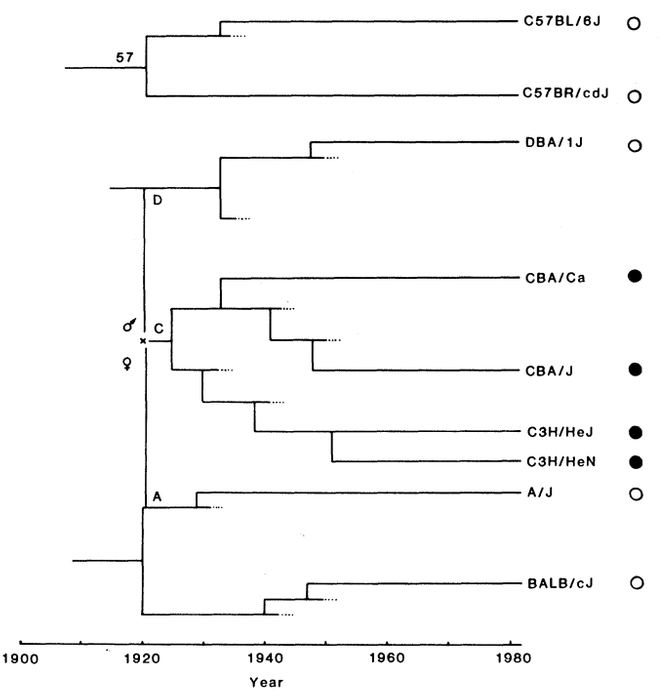

Fig. 1. The relationship between meprin deficiency and the origins of some inbred mouse strains. The genealogical chart was prepared from data in (*8, 9*). Strains that were classified as meprin-deficient are indicated on the right side by a closed circle; meprin-sufficient mice are indicated by an open circle. Ten years is approximately equal to 28 generations.

EGTA, 1,10-phenanthroline). Meprin is not, however, inhibited by phosphoramidon, a potent inhibitor of several other metalloendopeptidases (*4*). The broad substrate specificity, *p*H optimum, and refractivity to phosphoramidon distinguish meprin from other metalloendopeptidases purified from the kidneys of rabbit, pig, and rat (*4, 5*). In addition to meprin, phosphoramidon-inhibitable metalloendopeptidases, resembling those described in the other species, have been found in the kidneys of BALB/c mice (*6*).

We conducted studies on the distribution of meprin in mouse strains, using the substrate azocasein at *p*H 9.5. These assay conditions are particularly suitable for the determination of meprin because the contribution from other tissue proteinases is minimal (less than 5 percent of the total activity). There were marked differences in the specific activity of meprin (in homogenates or membrane preparations) between the various strains (Table 1). Although ten strains had specific activities similar to or higher than the BALB/c strain, the CBA/J, CBA/CaJ, and C3H/He activities were dramatically lower. The strains with low activity often included individual mice that had no detectable meprin activity. The meprin-sufficient strains of mice were resolved ($P < .01$) into a "high" and a "normal" group on the basis of Duncan's multiple range test (*7*). Specific activities of the high group (C57BL/6J, C57BR/cdJ, and B6C3F_1) were 50 percent higher than those of the normal group (BALB/c, A/J, DBA/1J, Swiss, ICR, and CD/1). By contrast, meprin was barely detectable in the deficient group, whose specific activities amounted to approximately 2 percent of those in the meprin-sufficient groups. The membrane preparations showed the expected twofold enrichment in meprin-specific activity and confirmed the separation of the strains into meprin-deficient and meprin-sufficient categories. The progeny (B6C3F_1) of a cross between a meprin-sufficient dam (C57BL/6Cr1) and a meprin-deficient sire (C3H/HeNCr1) contained a high specific activity of meprin, essentially identical to that of the dam. These data show that the trait for meprin deficiency is recessive.

We carried out a variety of experiments in an effort to detect an inhibitor of meprin in the CBA/J, CBA/CaJ, and C3H/He strains. We found that kidney homogenates of CBA/J or C3H/He mice mixed with those of BALB/c mice caused no suppression of the total proteolytic activity, and high-speed supernatant fractions from C3H/He mice incubated with membrane preparations from BALB/c mice demonstrated no inhibitory effects. A nonionic detergent [0.1 percent (weight/volume) Triton X-100] or high salt concentrations (1.0*M* NaCl) incubated with membrane preparations from meprin-deficient mice failed to produce any increase of measurable meprin activity that would have occurred if an inhibitor had been dissociated from the enzyme. Furthermore, meprin activity could not be detected in extracts from the deficient mice between *p*H 6.0 and 10.2 (we are excluding the possibility of an altered form of the enzyme that exhibited a shift in *p*H optimum). Reduction of meprin activity by combination with plasma proteinase inhibitors was unlikely since all the kidneys were perfused with saline prior to homogenization. On the basis of these data, we propose that the three unusual strains are deficient in catalytically active meprin.

Table 1. Specific activities of meprin in homogenates and membrane preparations of inbred mouse strains. The kidneys from mice (8 to 12 weeks) were perfused with 0.15*M* NaCl before dissection free of fat, adrenals, ureters, and capsule. Homogenates (20 percent, weight/volume) were prepared in ice-cold double-distilled water, and the membrane preparation, sedimenting between 100 and 100,000*g*-hour, was prepared. The activity of meprin in both preparations was determined at 37°C, *p*H 9.5, with azocasein (10 mg/ml) used as substrate (*3*); protein was measured according to the method of Lowry *et al.* (*12*). Specific activities are expressed as the mean ± standard deviation ($N = 4$) for each group of animals. The mice were male except where indicated. The sources of the animals were as follows: C57BL/6J, C57BR/cdJ, DBA/1J, C3H/HeJ (male), CBA/J, CBA/CaJ, A/J, and BALB/cJ (male) from Jackson Laboratory, Bar Harbor, Maine; C3H/HeN (female) (N substrain of the National Institutes of Health) and Swiss from Harlan–Sprague-Dawley, Gilbertsville, Pennsylvania; BALB/cCr1 (female), B6C3F_1/Cr1, and CD/1 from Charles River Breeding Laboratories, Wilmington, Massachusetts; and ICR from Dominion Laboratories, Dublin, Virginia.

Strain	Meprin-specific activity (units per mg protein)	
	Homogenate	Membrane preparation
Inbred strains		
C57BR/cdJ	6.46 ± 0.23	11.83 ± 0.42
C57BL/6J	6.35 ± 0.16	11.72 ± 0.49
B6C3F_1/Cr1*	5.91 ± 0.57	9.07 ± 0.72
BALB/cCr1 ♀	4.64 ± 0.31	8.58 ± 1.95
A/J	4.60 ± 0.19	9.27 ± 0.91
BALB/cJ	3.53 ± 0.40	8.78 ± 1.48
DBA/1J	3.28 ± 0.29	6.41 ± 0.98
CBA/J	0.09 ± 0.06	0.25 ± 0.07
C3H/HeN ♀	0.09 ± 0.04	0.15 ± 0.22
CBA/CaJ	0.08 ± 0.07	0.03 ± 0.04
C3H/HeJ	0.05 ± 0.04	0.02 ± 0.03
Random-bred strains		
CD/1	4.57 ± 0.65	6.51 ± 1.16
Swiss	4.42 ± 0.51	7.47 ± 0.81
ICR	3.46 ± 0.38	5.94 ± 1.38

*F_1 hybrid (see text).

The meprin-deficient strains are related genealogically (Fig. 1). All the deficient strains are derived from the original C stock established by Strong in 1922 (*8*) from a cross between a D stock mouse (progenitors of the DBA inbred strains) and a mouse from the then newly established A lineage (the forerunner of the A strains). Both DBA/1J and A/J mice have normal levels of meprin; this finding implies that the deficiency of meprin arose as an early event during the creation of the C lines, either as the result of a new mutation or as a consequence of the inheritance (and subsequent propagation) of this recessive characteristic from both parents. It is likely that neither of the parent lines was isogenic at the time of inception of the C linkage. Both of the inbred strains that were classified as containing high specific activities of meprin were derived from the C57 stock, established independently, and unrelated to the other strains.

We believe that this is the first demonstration of an inheritable deficiency of an integral cellular proteolytic activity. It is not clear whether (i) the kidney membrane contains a defective enzyme, (ii) the gene product is not synthesized, or (iii) meprin is degraded more rapidly than normal. The lack of expression of meprin activity in the CBA/J, CBA/CaJ, and C3H/He mice provides a valuable experimental system with which to assess the function of this recently discovered kidney metalloendopeptidase. There are no obvious differences in the viability or in the susceptibility to renal disease between meprin-deficient and meprin-sufficient animals (*9, 10*), and it is possible that other proteinases assume the role normally due to meprin. However, subtle differences in renal function between meprin-deficient and normal mice remain to be investigated. Inasmuch as many proteinases also possess esterase activity, it is conceivable that meprin may be one of the many "nonspecific esterases" that have been used in the study of enzyme polymorphism in the mouse (*11*). The ease of assay of meprin and its stability in tissue preparations indicate that it may find value in studies of mouse genetics.

ROBERT J. BEYNON
Department of Biochemistry, University of Liverpool, Post Office Box 147, Liverpool L69 3BX, United Kingdom
JUDITH S. BOND
Department of Biochemistry, Virginia Commonwealth University, Richmond 23298

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Spider Populations: Extraordinarily High Densities on Islands Without Top Predators

Abstract. *Distributions and densities of orb spiders on small islands are extremely variable. Species occurrences are far more irregular for spiders than vertebrates on the same islands. Much variation in spider density is explainable by distance from the presumed source of colonists and presence or absence of vertebrate predators. As has been predicted for passive dispersers, densities decline exponentially with distance. For a given distance, spider densities are about ten times greater on islands without vertebrate predators than on those with such predators.*

Predators that occupy intermediate trophic levels are ecologically ambiguous; should they resemble top carnivores or should they be strongly influenced by predation upon themselves and thereby resemble many herbivores (*1*)? One way to resolve this ambiguity is to compare populations of such predators with and without top carnivores. For this purpose, the inhabitants of small islands provide an ideal natural experiment. Our test organisms were orb-weaving spiders (Araneae), an abundant intermediate-level predator on subtropical islands. Numerous such islands suitable for spiders exist both with and without top carnivores, in this case lizards and birds.

We censused diurnal vertebrates and spiders on 93 neighboring Bahamian islands, chosen such that a substantial number were both just above and just below the minimal island size having any resident vertebrate species (*2*, *3*). We identified and counted spiders with webs on 80 of the islands; for the remaining 13, at least 60 percent of the island was censused and the total numbers of spiders were extrapolated. Four species—*Metepeira datona, Argiope argentata, Gasteracantha cancriformis, Eustala cazieri*—were common; a fifth—*Nephila clavipes*—occurred rarely. All resident vertebrates were lizards (*4*); in the general region, their densities are 10^{-1} to 10^{-2} per square meter.

Spiders occurred on smaller islands than did lizards. The smallest island with any spider species was 50 m^2 (vegetated area); other common species had only slightly larger minimal areas (55 to 112 m^2). The smallest island with a lizard population was 167 m^2; all larger islands also had lizards. All but two of the lizard-inhabited islands had the same species (*Anolis sagrei*), whereas any of the four spider species commonly occurred solitarily, a first indication of greater stochasticity in spiders. Below, we treat separately the 74 islands exceeding 50 m^2, the minimal area threshold for spiders [hereafter referred to as ST (spider threshold) islands], and the 55 islands exceeding the threshold (167 m^2) for lizards (hereafter referred to as LT islands).

We first made a number of simple analyses of covariance (ANCOVA's), using as the dependent variable either density or number of spiders of all species combined. When the effect of island area was taken into account, the number of spiders was smaller on islands with than without lizards (ST islands, $P = .02$; LT islands, $P = .02$; Fig. 1). Spider density was only slightly and negatively related to area; a negative relationship is to be expected given the statistical dependence of these two variables. When distance from a potential large source (*5*) was used as the continuous independent variable and spider density as the dependent variable, statistical significance was about the same as the previous analysis (ST islands, $P = .03$; LT islands, $P = .003$). Multiple ANCOVA's with spider number as the dependent variable and island area and distance as independent variables gave results no more significant than the simple

Table 1. Statistical analysis of factors affecting numbers of spiders on island. The N for ST was 74 and that for LT was 55. Abbreviations, *A*, area; *D*, distance; *M.d.*, *M. datona*; *G.c.*, *G. cancriformis*; *A.a*, *A. argentata*; *E.c.*, *E. cazieri*; *b* is a regression coefficient; S.E., standard error. Logs are to the base 10.

Dependent variable	Independent variables		Data set	Multiple ANCOVA P_F	Multiple regression									
					No-lizard islands					Lizard islands				
	X_1	X_2			b_1	S.E.$_1$	b_2*	S.E.$_2$*	r^2	b_1	S.E.$_1$	b_2*	S.E.$_2$*	r^2
Number spiders	*A*	*D*	ST	.010	0.03[d]	0.006	−122.4	117.7	0.32	0.004[c]	0.002	−155.1[b]	69.8	0.27
	A	*D*	LT	.011	0.03[b]	0.009	−140.2	173.3	0.28	0.004[c]	0.002	−155.1[b]	69.8	0.27
Log (number	log *A*	*D*	ST	$< 10^{-4}$	0.93[d]	0.160	−4.87[c]	1.55	0.45	0.73[c]	0.229	−6.55[c]	2.02	0.38
spiders + 1)†	log *A*	*D*	LT	$< 10^{-4}$	1.22[d]	0.295	−5.90[c]	1.91	0.45	0.73[c]	0.229	−6.55[c]	2.02	0.38
Log (all webs + 1)†	log *A*	*D*	ST	.020	1.06[d]	0.157	−2.28	1.52	0.50	0.89[d]	0.193	−2.92[a]	1.71	0.48
Log (*M.d.* + 1)†	log *A*	*D*	ST	.001	0.76[d]	0.174	−3.49[b]	1.68	0.31	0.28	0.242	−2.47	2.15	0.07
Log (*G.c.* + 1)†	log *A*	*D*	ST	.298	0.13	0.070	−0.66	0.682	0.07	0.43[b]	0.163	−3.29[b]	1.45	0.27
Log (*A.a.* + 1)†	log *A*	*D*	ST	.001	0.23[b]	0.108	−1.66	1.05	0.11	0.02	0.025	−0.22	0.224	0.05
Log (*E.c.* + 1)†	log *A*	*D*	ST	.511	0.15[b]	0.075	−0.58	0.725	0.09	0.23[a]	0.120	−2.20[b]	1.07	0.19

*To obtain true value, multiply by 10^{-4}. †We also added 0.1 and 0.01 to all log variables for most treatments. All F's significant at the 5 percent level were still significant, and vice versa. In multiple regressions, two distance coefficients not significant with 1.0 were significant with 0.01, and one distance coefficient was the opposite; all involve single-species data. In all cases, the significance of area coefficients was unaffected. In all cases, the sign of the effect was unchanged. [a].05 < P < .10. [b].01 < P < .05. [c].001 < P < .01. [d]P < .001.