Molecular Diversity (2006) 10: 511–514
DOI 10.1007/s11030-006-9048-y

Guest Editorial

Molecular diversity of proteins in biological offense and defense systems

Tomohisa Ogawa
Department of Biomolecular Science, Graduate School of Life Sciences, Tohoku University, Sendai, 981-8555, Japan (E-mail: ogawa@biochem.tohoku.ac.jp, Tel.: +81-22-7178808, Fax: +81-22-7178807)

The biodiversity of living organisms on Earth is the result of a perpetual evolutional process. One approach to tracing this process is through the application of currently available biomolecular techniques which, in particular, enable gene and protein sequences to be analyzed. The recent advances that have been made in a number of genome projects aimed at determining the genomes of various living species, including the human genome, have enabled scientists to view evolution within the framework of whole genome structures and, subsequently, be able to compare genomes between species.

To date, almost every study on molecular evolution has focused on individual genes or proteins. However, in order to be able to understand the evolutionary mechanism of diversified proteins in molecular networks, one must acquire a system-wide perspective, including the us-or-them war of survival. One of the important questions in molecular evolution is: How can new adaptations to proteins recognize the target molecules to be obtained in the complex biological networks? An applicable example of the evolutionary mechanism at work are adaptations in network, biological defense and offense systems. These two systems are essentially equal and identical with the exception of the target protein; i.e. biological defense molecules such as anti-bacterial proteins are produced in humans as offensive molecules against bacteria; conversely, the bacterial toxins are offensive molecules against humans but defensive molecules for the bacterial cell itself. Interactions between species, such as paragenetic and hostile correlations, must affect the evolutional processes of the interacting species.

The mechanism by which genes and proteins have evolved in a molecular context is believed to be through the fixation and chance adaptation of errors that occurred in the genome during gene replication and/or repair. Alternative splicing and gene duplication are well-known major mechanisms for generating new functional and evolutionary molecular diversities of proteins [1, 2]. More recently, some hot topics have attracted the attention of many researchers: the role of gene duplication in the emergence of novel functions, adaptive molecular evolution versus neutral drift and the identification of molecular evolutional pathways responsible for various human characteristics pertaining to infection and disease. Rapid adaptive evolution, which is characterized by a higher mutation rate of non-synonymous nucleotides (causing amino acid change) to synonymous ones (not causing amino acid change) and/or by the higher mutation rate of coding region/exons compared to those of non-coding/introns, has been identified in several gene families, including that of 'Biological offense & defense systems' and 'Reproduction' (see Table 1 and Ref. [59–61]).

In this special issue of *Molecular Diversity*, we focus on the molecular evolution of proteins in biological offense and defense systems: vascular endothelial growth factor (VEGF) family proteins and their receptors, including recently identified snake venom-derived VEGFs (Yasuo Yamazaki and Takashi Morita), snake neurotoxins (Toru Tamiya and Takahiko J. Fujimi) and spider toxins (Pierre Escoubas) in biological offense systems. Furthermore, five unique examples of biological defense systems are described: adaptive rapid evolution of the Siglec family of cell-surface lectins (Takashi Angata), conger eel galectins (Tsuyoshi Shirai et al.), β-defensins (Julia R. Dorin and Colin Semple), RNase A superfamily (Kimberly Dyer and Helene F. Rosenberg) and insects' immunoglobulin superfamily (Shoichiro Kurata). Thus, the readers will be able to get an overall feeling for the field in general as well as acquire some insight into each unique case of proteins in biological offense and defense systems and, consequently into the molecular evolution of proteins. This special issue will no doubt provide interesting reading material.

I would like to thank to contributors for their support, and also gratefully acknowledge the help received from the reviewers in evaluating the manuscripts. Many thanks are also extended to professor Dr. Shu-Kun Lin (Editor-in-Chief) for his assistance.

Table 1. Examples of proteins/genes in which adaptive evolution has been detected

Genes/proteins	Gene duplication (GD)	Organism	Reference
Biological offense & defense systems			
Parasitic, pathogenic antigen			
Hemagglutinin/gp120/VP1/gH/S & HE glycoprotein/delta-antigen		Virus	[3–6]
Porin protein 1		Bacteria (*Neisseria*)	[7]
CSP, TRAP, MSA-2 & PF83		Protozoa	[8]
Resistance to antibiotics			
β-lactamase		Bacteria (TEM)	[9]
Toxin			
Colicin		Bacteria	[10]
Conotoxins	GD	Mollusc (*Conus*)	[11–14]
Phospholipase A2/Serine protease/Zn protease/*3 finger toxins*/CTLP	GD	Reptile (Snake)	[15–20]
Spider toxins/Scorpion toxins	GD	Arthropod	[21–24]
Immunity			
Immunoglobulin VH	GD	Mammals	[25]
MHC	GD	Mammals	[26]
Enzyme inhibitors			
α1-Proteinase inhibitor	GD	Rodents	[27]
Elafin	GD	Mammals	[28]
Polygalacturonase inhibitor		Plant (Legume)	[29]
Type I interferon-omega		Mammals	[30]
Phospholipase A2 inhibitor	GD	Reptile (Snake)	[31]
Innate immunity			
Siglec	GD	Mammals	[32]
Class1 chitinase		Plant (*Arabidopsis*)	[33]
Congerins	GD	Fish	[34, 35]
Transferrin		Fish	[36]
Defensin	GD	Mammals	[37, 38]
RH, RH50 blood group	GD	Primates and rodents	[39]
RNase A	GD	Mammals	[40, 41]
Cytidine deaminase		Mammals	[42]
Reproduction			
Cell recognition			
18-kDa fertilization protein/Sperm lysin/TMAP/lysine-R		Mollusc (*Haliotis*)	[43–45]
Bindin/suREJ		Echinoderm	[46, 47]
Protamine P1		Primates	[48]
ZP2/ZP3		Rodents	[49]
S-Rnase	GD	Plant	[50]
Reproduction behavior control			
Acp26Aa, Acp70A	GD	Drosophila	[51]
Androgen-binding protein		Rodents	[52]
Reproductive transcription factor			
Sry gene		Primates	[53]
Ods homeobox		*Drosophila*	[54]
Pem homeobox	GD	Rodents	[55]
Others			
Transcription factor Asr2		Plant (*Lycopersicon*)	[56]
Fatty acid synthase		Human	[57]
Pten gene		Insects	[58]

References

1. Kriventseva, E.V., Koch, I., Apweiler, R., Vingron, M., Bork, P., Gelfand, M.S. and Sunyaev, S., *Increase of functional diversity by alternative splicing*, Trends Genet. 19 (2003) 124–128.
2. Su, Z., Wang, J., Yu, J., Huang, X. and Gu, X., *Evolution of alternative splicing after gene duplication*, Genome Res. 16 (2006) 182–189.
3. Fitch, W.M., Bush, R.M., Bender, C.A. and Cox, N.J., *Long term trends in the evolution of H(3) HA1 human influenza type A*, Proc. Natl. Acad. Sci., USA 94 (1997) 7712–7718.
4. Endo, T., Ikeo, K. and Gojobori, T., *Large-scale search for genes on which positive selection may operate*, Mol. Biol. Evol. 13 (1996) 685–690.
5. Baric, R.S., Yount, B., Hensley, L., Peel, S.A. and Chen W.l., , *Episodic evolution mediates interspecific transfer of a murine coronavirus*, J. Virol. 71 (1997) 1946–1955.
6. Wu, J.C., Chiang, T.Y., Shiue, W.K., Wang, S.Y., Sheen, I.J., Huang, Y.H. and Syuet, W.J., *Recombination of hepatitis D virus RNA sequences and its implications*, Mol. Biol. Evol. 16 (1999) 1622–1632.
7. Smith, N.H., Maynard Smith, J. and Spratt, B.G., *Sequence evolution of the porBgene of Neisseria gonorrhoeae and Neisseria meningitidis: evidence for positive darwinian selection*, Mol. Biol. Evol. 12 (1995) 363–370.
8. Hughes, M.K. and Hughes, A.L., *Natural selection on Plasmodium surface proteins*, Mol. Biochem. Parasitol. 71 (1995) 99–113.
9. Weinreich, D.M., Delaney, N.F., DePristo, M.A. and Hartl, D.L., *Darwinian evolution can follow only very few mutational paths to fitter proteins*, Science 312 (2006) 111–114.
10. Riley, M.A., *Positive selection for colicin diversity in bacteria*, Mol. Biol. Evol. 10 (1993) 1048–1059.
11. Duda, T.F. and Palumbi, S.R. Jr., *Molecular genetics of ecological diversification: duplication and rapid evolution of toxin genes of the venomous gastropod Conus*, Proc. Natl. Acad. Sci. USA 96 (1999) 6820–6823.
12. Duda, T.F. and Palumbi, S.R. Jr., *Evolutionary diversification of multigene families: allelic selection of toxins in predatory cone snails*, Mol. Biol. Evol. 17 (2000) 1286–1293.
13. Conticello, S.G., Gilad, Y., Avidan, N., Ben-Asher, E., Levy, Z. and Fainzilber, M., *Mechanisms for evolving hypervariability: the case for conopeptides*, Mol. Biol. Evol. 18 (2001) 120–131.
14. Olivera, B.M., Walker, C., Cartier, G.E., Hooper, D., Santos, A.D., Schoenfeld, R., Shetty, R., Watkins, M., Bandyopadhyay, P. and Hillyard, D.R., *Speciation of cone snails and interspecific hyperdivergence of their venom peptides: potential evolutionary significance of introns*, Ann. N.Y. Acad. Sci. 870 (1999) 223–237.
15. Nakashima, K., Ogawa, T., Oda, N., Hattori, M., Sakaki, Y., Kihara, H. and Ohno, M., *Accelerated evolution of Trimeresurus flavoviridis venom gland phospholipase A_2* isozymes, Proc. Natl. Acad. Sci. USA 90 (1993) 5964–5968.
16. Nakashima, K., Nobuhisa, I., Deshimaru, M., Nakai, M., Ogawa, T., Shimohigashi, Y., Fukumaki, Y., Hattori, M., Sakaki, Y., Hattori, S. and Ohno, M., *Accelerated evolution in the protein-coding regions is universal in crotalinae snake venom gland phospholipase A_2* isozyme genes, Proc. Natl. Acad. Sci. USA 92 (1995) 5605–5609.
17. Deshimaru, M., Ogawa, T., Nakashima, K., Nobuhisa, I., Chijiwa, T., Shimohigashi, Y., Fukumaki, Y., Niwa, M., Yamashina, I., Hattori, S. and Ohno, M., *Accelerated evolution of crotalinae snake venom gland serine proteases*, FEBS Lett. 397 (1996) 83–88.
18. Calvetea, J., Marcinkiewiczb, C., Monleónc, D., Esteveac, V., Celdaçd, B., Juáreza, P. and Libia Sanz, L., *Snake venom disintegrins: evolution of structure and function*, Toxicon 45 (2005) 1063–1074.
19. Ohno, M., Menez, R., Ogawa, T., Danse, J.M., Shimohigashi, Y., Fromen, C., Ducancel, F., Zinn-Justin, S., Le Du, M.H., Boulain, J.C., Tamiya, T. and Menez, A., *Molecular evolution of snake toxins: is the functional diversity of snake toxins associated with a mechanism of accelerated evolution?*, Prog. Nucleic Acids Res. Mol. Biol. 59 (1998) 307–364.
20. Ogawa, T., Chijiwa, T., Oda-Ueda, N. and Ohno, M., *Molecular diversity and accelerated evolution of C-type lectin-like proteins from snake venom*, Toxicon 45 (2005) 1–14.
21. Froy, O., Sagiv, T., Poreh, M., Urbach, D., Zilberberg, N. and Gurevitz, M., *Dynamic diversification from a putative common ancestor of scorpion toxins affecting sodium, potassium, and chloride channels*, J. Mol. Evol. 48 (1999) 187–196.
22. Zhu, S., Bosmans, F. and Tytgat, J., *Adaptive evolution of scorpion sodium channel toxins*, J. Mol. Evol. 58 (2004) 145–153.
23. Cao, Z., Mao, X., Xu, X., Sheng, J., Dai, C., Wu, Y., Luo, F., Sha, Y., Jiang, D. and Li, W., *Adaptive evolution after gene duplication in alpha-KT x 14 subfamily from Buthus martensii Karsch*, IUBMB Life. 57 (2005) 513–521.
24. Escoubas, P., Diochot, S. and Corzo, G., *Structure and pharmacology of spider venom neurotoxins*, Biochimie 82 (2000) 893–907.
25. Tanaka, T. and Nei, M., *Positive darwinian selection observed at the variable-region genes of immunoglobulins*, Mol. Biol. Evol. 6 (1989) 447–459.
26. Hughes, A.L. and Nei, M., *Pattern of nucleotide substitution at major histocompatibility complex class I loci reveals overdominant selection*, Nature 335 (1988) 167–170.
27. Goodwin, R.L., Baumann, H. and Berger, F.G., *Patterns of divergence during evolution of* α1-proteinase inhibitors in mammals, Mol. Biol. Evol. 13 (1996) 346–358.
28. Tamechika, I., Itakura, M., Saruta, Y., Furukawa, M., Kato, A., Tachibana, S. and Hirose, S., *Accelerated evolution in inhibitor domains of porcine elafin family members*, J. Biol. Chem. 271 (1996) 7012–7018.
29. Stotz, H.U., Bishop, J.G., Bergmann, C.W., Koch, M., Albersheim, P., Darvill, A.G. and Labavitchet, J.M., *Identification of target amino acids that affect interactions of fungal polygalacturonases and their plant inhibitors*, Mol. Physiol. Plant Pathol. 56 (2000) 117–130.
30. Hughes, A.L., *The evolution of the type I interferon family in mammals*, J. Mol. Evol. 41 (1995) 539–548.
31. Nobuhisa, I., Deshimaru, M., Chijiwa, T., Nakashima, K., Ogawa, T., Shimohigashi, Y., Fukumaki, Y., Hattori, S., Kihara, H. and Ohno, M., *Structures of genes encoding phospholipase A2 inhibitors from the serum of Trimeresurus flavoviridis snake*, Gene 191 (1997) 31–37.
32. Angata, T., Margulies, E.H., Green, E.D. and Varki, A., *Large-scale sequencing of the CD33-related Siglec gene cluster in five mammalian species reveals rapid evolution by multiple mechanisms*, Proc. Natl. Acad. Sci. USA 101 (2004) 13251–13256.
33. Bishop, J.G., Dean, A.M. and Mitchell-Olds, T., *Rapid evolution in plant chitinases: molecular targets of selection in plant–pathogen coevolution*, Proc. Natl. Acad. Sci. USA 97 (2000) 5322–5327.
34. Ogawa, T., Ishii, C., Kagawa, D., Muramoto, K. and Kamiya, H., *Accelerated evolution in the protein-coding region of galectin cDNAs, congerin I and congerin II, from skin mucus of conger eel (Conger myriaster)*, Biosci. Biotechnol. Biochem. 63 (1999) 1203–1208.
35. Ogawa, T., Shirai, T., Shionyu-Mitsuyama, C., Yamane, T., Kamiya, H. and Muramoto, K., *The speciation of conger eel galectins by rapid adaptive evolution*, Glycoconj. J. 19 (2004) 451–458.
36. Ford, M.J., *Molecular evolution of transferrin: evidence for positive selection in salmonids*, Mol. Biol. Evol. 18 (2001) 639–47.

37. Semple, C.A., Rolfe, M. and Dorin, J.R., *Duplication and selection in the evolution of primate beta-defensin genes*, Genome Biol. 4 (2003) R31.
38. Lynn, D.J., Lloyd, A.T., Fares, M.A. and O'Farrelly, C., *Evidence of positively selected sites in mammalian alpha-defensins*, Mol. Biol. Evol. 21 (2004) 819–827.
39. Kitano, T. and Saitou, N., *Evolution of Rh blood group genes have experienced gene conversions and positive selection*, J. Mol. Evol., 49 (1995)615–626.
40. Zhang, J., Rosenberg, H.F. and Nei, M., *Positive darwinian selection after gene duplication in primate ribonuclease genes*, Proc. Natl. Acad. Sci. USA 95 (1998) 3708–3713.
41. Zhang, J., Zhang, Y.P. and Rosenberg, H.F., *Adaptive evolution of a duplicated pancreatic ribonuclease gene in a leaf-eating monkey*, Nat. Genet. 30 (2002) 411–415.
42. OhAinle, M., Kerns, J.A., Malik, H.S. and Emerman, M., *Adaptive evolution and antiviral activity of the conserved mammalian cytidine deaminase APOBEC3H*, J. Virol. 80 (2006) 3853–3862.
43. Vacquier, V.D., Swanson, W.J. and Lee, Y.H., *Positive darwinian selection on two homologous fertilization proteins: what is the selective pressure driving their divergence?*, J. Mol. Evol. 44 (1997) 15–22.
44. Hellberg, M.E., Moy, G.W. and Vacquier, V.D., *Positive selection and propeptide repeats promote rapid interspecific divergence of a gastropod sperm protein*, Mol. Biol. Evol. 17 (2000) 458–466.
45. Galindo, B.E., Vacquier, V.D. and Swanson, W.J., *Positive selection in the egg receptor for abalone sperm lysine*, Proc. Natl. Acad. Sci. USA 100 (2003) 4639–4643.
46. McCartney, M.A. and Lessios, H.A., *Adaptive evolution of sperm bindin tracks egg incompatibility in neotropical sea urchins of the genus Echinometra*, Mol. Biol. Evol. 21 (2004) 732–745.
47. Mah, S.A., Swanson, W.J. and Vacquier, V.D., *Positive selection in the carbohydrate recognition domains of sea urchin sperm receptor for egg jelly (suREJ) proteins*, Mol. Biol. Evol. 22 (2005) 533–541.
48. Rooney, A.P. and Zhang, J., *Rapid evolution of a primate sperm protein: relaxation of functional constraint or positive darwinian selection?* Mol. Biol. Evol. 16 (1999) 706–710.
49. Turner, L.M. and Hoekstra, H.E., *Adaptive evolution of fertilization proteins within a genus: Variation in ZP2 and ZP3 in Deer Mice (Peromyscus)*, Mol. Biol. Evol., 23 (2006) 1656–1669.
50. Ishimizu, T., Endo, T., Yamaguchi-Kabata, Y., Nakamura, K.T., Sakiyama, F. and Norioka, S., *Identification of regions in which positive selection may operate in S-RNase of Rosaceae: implications for S-allele-specific recognition sites in S-Rnase*, FEBS Lett. 440 (1998) 337–342.
51. Tsaur, S.C. and Wu, C-I., *Positive selection and the molecular evolution of a gene of male reproduction, Acp26Aa of Drosophila*, Mol. Biol. Evol. 14 (1997) 544–549.
52. Karn, R.C. and Nachman, M.W., *Reduced nucleotide variability at an androgen-binding protein locus (Abpa) in house mice: evidence for positive natural selection*, Mol. Biol. Evol. 16 (1999) 1192–1197.
53. Pamilo, P. and O'Neill, R.W., *Evolution of Sry genes*, Mol. Biol. Evol. 14 (1997) 49–55.
54. Ting, C.T., Tsaur, S.C., Wu, M.L. and Wu, C.I., *A rapidly evolving homeobox at the site of a hybrid sterility gene*, Science 282 (1998) 1501–1504.
55. Sutton, K.A. and Wilkinson, M.F., *Rapid evolution of a homeodomain: evidence for positive selection*, J. Mol. Evol. 45 (1997) 579–588.
56. Frankel, N., Hasson, E., Iusem, N.D. and Rossi, M.S., *Adaptive evolution of the water stress-induced gene Asr2 in Lycopersicon species dwelling in arid habitats*, Mol. Biol. Evol. 20 (2003) 1955–1962.
57. O'Connell, M.J. and McInerney, J.O., *Adaptive evolution of the human fatty acid synthase gene: support for the cancer selection and fat utilization hypotheses?*, Gene 360 (2005) 151–159.
58. Baudry, E., Desmadril, M. and Werren, J.H., *Rapid adaptive evolution of the tumor suppressor gene pten in an insect lineage*, J. Mol. Evol. 62 (2006) 738–744.
59. Yang, Z. and Bielawski, J.P., *Statistical methods for detecting molecular adaptation*, TREE 15 (2000) 496–503.
60. Swanson, W.J., *Adaptive evolution of genes and gene families*, Curr. Opin. Genet. Develop. 13 (2003) 617–622.
61. Swanson, W.J. and Vacquier, V.D., *The rapid evolution of reproductive proteins*, Nat. Rev. Genet. 3 (2002) 137–144.