Mammalian Evolution elucidated from the study of SINEs

Norihiro Okada

Tokyo Institute of Technology

SINEs stands for short interspersed elements, one of retroposons that can amplify themselves in the genomes. SINEs was originally thought to be selfish genetic elements and not functional, and their insertion sites are random during evolution. By using these characteristics, we have developed the reliable method to determine phylogenetic relationships. By applying this method, so called the SINE method (1), to the mammalian phylogeny, we solved long-standing phylogenetic questions such as the origin of whales (2,3), the phylogenetic position of bats (4) and the divergence order of primitive eutherian mammals (5).

Recently, thanks to the development of genomics, CNEs (conserved non-coding-elements) were discovered. CNEs are now considered to be a key element for macro-evolution. we discovered that AmnSINE1s are a part of mammalian-specific CNEs, suggesting that AmnSINEs got functions in a common ancestor of mammals that are mammalian-specific (6). In the Sasaki et al.'s PNAS paper (7), we elucidated that SINE loci function as enhancers for fgf8 and satb2. In the human genome, there are more than 100 loci of AmnSINE1s, so it will be very interesting for us to elucidate these all functions, because we will be able to describe the whole story of how mammalian-specific phenotypes were generated on the DNA level.

Especially, I link this event to the famous geological event occurred at 250 million years ago (Ma), which is called P-T mass extinction. At that time, it is believed that almost 96% species were extinct. Therefore, even survivals had hard time to live and they should have adapted to the extreme environmental conditions. Accordingly, at that time, many interesting exaptation events should have occurred on the DNA level. Actually, we recently discovered that an AmnSINE1 functions as an enhancer for wint5a, which is responsible for closure of the secondary palate of mammals. Closure of the secondary palate is specific for mammals, and responsible for establishment of efficiency of respiration. Therefore, this is considered to be adaptation for low-concentration of oxygen, which is actually demonstrated to have occurred after P-T mass extinction. I therefore consider that the AmnSINE1 locus got function as an

enhancer for Wint5a to adapt this anoxia condition by exaptation. Another example is that of satb2. We recently elucidated, in collaboration with Prof. Alessandra Pierani, a neurobiologist in Jacques-Monod Institute, that this SINE is specifically responsible for extension of axons into corpus callosum through enhancement of satb2 expression. Corpus callosum is an organ mammalian-specific, so getting function of this SINE is considered to be one of the exaptations occurred at 250 Ma (8). These examples now provide myself a belief that this project will be very fruitful and contributes to the science greatly.

(1) **Shedlock, A.M., and Okada, N. (2000) SINE Insertions : Powerful Tools for Molecular Systematics. BioEssays. 22, 148-160.**

(2) **Shimamura, M., Yasue, H., Ohshima, K., Abe, H., Kato, H., Kishiro, T., Goto, M., Munechika, I., and Okada, N. (1997) Molecular evidence that whales form a clade within even-toed ungulates. Nature. 388, 666-670.**

(3) **Nikaido, M., Rooney, A.P., and Okada, N. (1999) Phylogenetic relationships among cetartiodactyls based on insertions of short and long interspersed elements: Hippopomamuses are the closest extant relatives of whales. Proc. Natl. Acad. Sci. USA. 96, 10261-10266.**

(4) **Nishihara, H., Hasegawa, M., and Okada, N. (2006) Pegasoferae, an unexpected mammalian clade revealed by tracking ancient retroposon insertions. Proc Natl Acad Sci USA. 103, 9929-9934.**

(5) **Nishihara, H., Maruyama, S., Okada, N. (2009) Retroposon analysis and recent geological data suggest near-simultaneous divergence of the three superorders of mammals. Proc. Natl Acad Sci USA. 106, 5235-5240.**

(6) **Nishihara, H., Smit, A.F., and Okada, N. (2006) Functional noncoding sequences derived from SINEs in the mammalian genome. Genome Res. 22, 864-874.**

(7) **Sasaki, T., Nishihara, H., Hirakawa, M., Fujimura, K., Tanaka, M., Kokubo, N., Kimura-Yoshida, C., Matsuo, I., Sumiyama, K., Saitou, N., Shimogori, T., and Okada N. (2008) Possible involvement of SINEs in mammalian-specific brain formation. Proc Natl Acad Sci USA. 105, 4220-4225.**

(8) Submitted