

Mitochondria and mind

Mitochondria are well known as the powerhouse of the cell. Recent work shows that in addition, these symbiotic organelles, which are very likely derived from an independently existing ancestor (Margulis 1993), can play a role in learning, memory and cognition.

The role of mitochondria in brain disorders of mice and men was reported five years ago by Wallace (1999); also, memory loss in old rats has been associated with mitochondrial decay (Liu *et al* 1999). Roubertoux *et al* (2003) tried to provide direct evidence for the role played by mitochondrial DNA in cognitive functions. Their basic approach is beautiful in its simplicity. In order to separate the effects of nuclear and mitochondrial DNA, they adopted the following strategy while cross breeding two strains of mice, *Mus musculus domesticus* and *Mus musculus brevisrostris*. Let us denote the two strains by *AH* and *BN* where *A* and *B* are the nuclear and *H* and *N*, the corresponding mitochondrial (mt) genomes. Since mt DNA is transmitted through the mother only, four types of nuclear and mt DNA combinations are possible, the two original combinations and two new products of hybridization. A female *AH* × male *BN* cross would lead to $(1/2 A + 1/2 B) H$ in the first filial generation, because all the offspring would inherit the mother's mt DNA, namely *H*. Back-crossing the female offspring with *BN* would increase the amount of the nuclear B genome. For example, the next cross would yield $(1/4 A + 1/4 B + 1/2 B) H$ or $(1/4 A + 3/4 B) H$. Since mice have about 30000 genes, 20 such back crossings would be expected to result in (an average of) $1/2^{20} \times 30000$, or less than one nuclear gene of *A* in the progeny. This procedure yields what is, for all practical purposes, the new strain *BH*. Likewise, the strain *AN* can be established. So, we now have the quartet *AH*, *BN* and the new combinations *BH* and *AN*.

It was verified that mitochondrial DNA is actually expressed in the brain cells formed by the old strains. Sequencing confirmed that the mitochondrial DNA was identical in *AH* and *BH* or *AN* and *BN* mice. The difference in base sequences in the two sorts of mitochondria was pinpointed to substitutions such as A instead of T or C instead of T. 13 mt genes were noted as being expressed in the brain cells of the four strains of mice. The polypeptides encoded by these genes were studied and it was shown that 6 of the 13 genes led to identical products (identical amino acids) in both strains while 7 genes produced polypeptides differing in certain amino acids. So at the protein level, the difference in the mt DNA is traceable to these changed amino acids in their products. This relatively minor polymorphism in mt DNA seems to have profound implications.

The four strains of mice were now subjected to standard tests that animal psychologists have been using over many years. Radial mazes with different paths are well known; the animals learn to find the right or quickest way. The Morris maze is also commonly used. Here a shelf or stepping stone lies below the water level but is invisible because the water is turbid. An animal that is dropped into the water swims at random till it finds the shelf and rests there. Afterwards it learns the orientation of the shelf with respect to visible reference objects, and improves its score. In sets of experiments using these two and yet another method (Krushinsky's test), a remarkable fact was unearthed. In all tests, mice with one of the two mt genomes, namely *N*, show poor performance. This conclusion could be drawn because it was possible to observe the nuclear and mt genomes for their effects in different combinations. The mt DNA of *N*, for example, is not interacting with the nuclear DNA(*B*) in the new strain *AN*. Thus, with the help of the four strains, we can distinguish the contributions of mt DNA *per se*. The rather slight polymorphism (*A* and *H*) leads to a marked difference in cognitive abilities. Thus mental feat is at least partly due to mt DNA. Exploratory activity is affected by an interaction of nuclear and mt DNA. The new strains (new combinations of nuclear and mt DNA) have lower exploratory behaviour but within the experimental paradigms used, mt DNA seems to play no role in aggression, anxiety or maternal behaviour.

By comparing the performance of 6 and 12 month old batches of mice it has been shown that aging causes poor performance; more so, the lower efficiency of *N* is accentuated with age. This is in conformity with the earlier findings of Enard *et al* (2002) and Liu *et al* (2002), namely that mitochondrial decay is correlated with an age-dependent deterioration of cognitive ability.

Given these and other findings not mentioned here, we have to consider the fact that mt DNA has a role to play in moulding mental faculties. This is interesting by itself. It is doubly so viewed from an evolutionary perspective. Over aeons of symbiotic evolution mitochondria, initially foreign bodies, have come to influence our mental faculties

How exactly mitochondria play a role, is not clear. It is known, however, that mitochondria contribute to synaptic plasticity (Weeber *et al* 2002; Leavy *et al* 2003). This may be a pointer to future advances in the field.

References

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