Comparative Genomics of OXPHOS gene families

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Motivation

The gene transfer from the primitive mitochondrion to the nucleus stopped in the 800 Myr of Metazoan evolution, freezing the mitochondrial shape and size (with few exceptions) and reducing the gene content to a small contribution. The evolution of the mitochondrial genome and its dynamics has been extensively studied, also by our research group[1-3], but mitochondrial biogenesis and function are complex processes still far from being completely understood. The complete protein complement of mitochondria has still to be identified with both experimental and computational approaches having been applied to predict its quantitative value. It is currently rated at about 600-750 different proteins in yeast[4] and 600-1300 proteins for the human organelle[5]. Consequently, it is evident that the number of nuclear encoded proteins for the mitochondrion, even if still uncertain, is more than one, probably two order of magnitude higher than the number of mitochondrially encoded proteins. In this context, it seems clear that both the evolution and function of the mitochondrion itself and of the whole cell must be subject to forces modulating the interaction between the two genomes. In order to investigate the evolutionary relationship between mitochondrial and nuclear genomes, we have focused our attention on nuclear gene families involved in the main mitochondrial function, i.e OXPHOS (Oxidative Phosphorylation). We have observed that OXPHOS nuclear genes have a lower trend to produce or preserve duplications in Metazoa [6] Here we report the phylogenetic analysis of some OXPHOS gene families: LBP carrier and Cytochrome c (Cytc), which are instead subject to a higher expansion trend. The integrated phylogenetic and expression analysis of these large OXPHOS gene families could lead to a better understanding of their high expansion trend and could be useful to investigate and correlate the expression level of gene family members with a tissue specific and/or developmentally specific role.

Methods

Sequence data All Metazoan members of the LBP gene family were retrieved using the human protein sequences P1, P2 and P3 as query for TBlastN search on cDNA databases of 16 Metazoa. Cytc protein sequences, already annotated in the SWISSPROT and NCBI database, were collected and used as TBlastN queries to search for duplicated genes in the ENSEMBL database on cDNA databases of 19 Metazoa. All the source transcripts are shown in De Grassi et al. paper[7] Phylogenetic analysis Protein sequences were multialigned and the alignments of nucleotide sequences were deduced by over-imposing protein multi-alignment. The full alignment length is: 153aa for LBP sequences and 121aa for Cytc sequences.. The Bayesian analysis was carried out using the MrBayesv3.0b4 program, with the General-Time-Reversible substitution model[1] for nucleotide sequences and the Dayhoff model for protein sequences.

Results

A peculiar property of LBP is that it is mitochondrially encoded in yeast (e.g. S. cerevisiae and S. pombae), while it has been transferred to the nuclear genome both in plants and animals. In the human genome, LBP is represented by a gene family of three members encoding three different isoforms (P1, P2 and P3). Cytc is a central component of the electron transfer chain and is involved in both aerobic and anaerobic respiration. It also takes part in other cellular processes such as apoptosis and heme biosynthesis. Both the LBP and Cytc gene families are exceptions to the general rule for which OXPHOS genes are under-duplicated in Metazoan genomes[7]. The phylogenetic analysis of the ATP synthase LBP suggests that (1) the three isoforms were already present before the Birds-Mammals divergence, (2) only the P3 isoform possesses a putative orthologous gene in all analysed Vertebrates and (3) the P1 isoform is the most evolutionary divergent. In addition, in silico analysis has shown that: (4) P1 has a lower expression level than P2 and P3 isoforms both in man and mouse and (5) P1 is not in the NRF1 regulation circuit. Further

studies will be required to define the specific role of the three LBP gene family members, but we observed that the P1 isoform possesses evolutionary and functionally divergent features. Our analysis of the Cytc gene family give important additional information to previous studies. On the whole, this study underlines that the evolutionary history of these two gene families has followed a completely different destiny in Mammals: (1) the LBP gene family is highly conserved, presenting three functional isoforms in all the analysed Mammals and P1 specific features, common to both human and mouse genomes; (2) in contrast, the Cytc gene family has been subject to complex genomic and functional events only in Mammals, leaving a unique somatic isoform in the human genome and, at least, two functional isoforms (somatic and testis-specific) in rodent genomes, which has been previously found in all OXPHOS duplicated genes in Insects[8]

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