Histidine biosynthesis: a paradigm for the study of the origin and

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Motivation

The investigation of the origin and evolution of metabolic pathways represents a key step towards the understanding of cell evolution. Even though several theories have been proposed to explain the origin of basic metabolic routes, both sequence comparisons and directed evolution experiments support the so-called 'Patchwork hypothesis' (Jensen, 1976). Accordingly, primitive cells contained few genes coding for enzymes endowed with low substrate specificity and involved in different metabolic pathways. Paralogous duplication followed by evolutionary divergence of these genes lead to the narrowing of substrate specificity of their products and to the gaining of new metabolic abilities. These new genes might have also been recruited in diverse metabolic routes. One of the most interesting study-model is histidine biosynthesis, which is a main cross-lights for many biosynthesis and very likely was assembled before the appearance of the last universal common ancestor (LUCA). The integration of data coming from the analysis of his genes structure, organization and regulation of several different organisms belonging to the three cell domains (Archaea, Bacteria and Eucarya) whose genome has been completely sequenced allowed tracing the evolutionary history of this pathway.

Methods

Structure comparisons were performed using SwissPDB viewer (Guex et al. 1997).
Phylogenetic analyses were performed using MrBayes with different evolutionary methods, gamma-distributed rates and empirical aminoacid frequencies. Multialignments were performed using Muscle3.6 (Edgar 2004). Position Weight Matrices of his leader genes were obtained with self-written java code. A modification of MotifScorer (Brilli et al., 2007) was used to scan his genes and identify putative attenuators.

Results

Structure of his genes Gene elongation A gene elongation event results from in tandem duplication of a gene followed by the fusion of the two copies; this leads to a new gene with two paralogous moieties. It is likely that gene elongation played crucial role in genes evolution. This is also true for at least four his genes: hisA, hisF, hisB and hisD. The genes hisA and hisF represent a key gene elongation/gene duplication paradigm because they are the outcome of a cascade of gene elongation and duplication events. According to the model proposed an ancestral gene a quarter the size of the extant hisA and hisF underwent two elongations event, followed by a gene duplication, originating the ancestor of hisA and hisF. Gene fusions Several his genes underwent different gene fusions events in diverse (micro)organisms, as reported below: 1) a fusion involving hisI and hisE was disclosed in some Archaea, in Firmicutes, Cyanobacteria, and gamma-and epsilon-proteobacteria. This gene fusion might represent a paradigmatic example of a phenomenon of divergent/convergent evolution, and horizontal gene transfer; 2) hisNB is a recent invention of evolution; indeed the appearance of this fused gene can be dated in the ancestor of the gamma-proteobacteria. The evolutionary history of the hisN moiety is rather intriguing; this gene codes for a histidinol phosphate phosphatase (HOL-Pase). It is known that at least three different HOL-Pases are involved in histidine biosynthesis in different organisms. We determined the phylogenetic distribution of these enzymes and depicted an evolutionary model according to which the LUCA harbored different aspecific enzymes catalyzing HOL-P dephosphorylation.
Gene organization We found that after the divergence of Bacteria and Archaea from LUCA, different (micro)organisms adopted diverse his gene organization strategies. The his genes can be: i) clustered in operons with different extents of compactness; ii) scattered throughout the genome, or iii) partially clustered/scattered. However, some extant compact his operons appeared to be a recent invention of evolution and were constructed starting from scattered genes through a piece-wise mechanism.
Regulation of his genes In E. coli different mechanisms to tune finely histidine biosyntesis have been disclosed. One of them is represented by the feedback inhibition by histidine of the first enzyme (ATP-PRTase) of the biosynthetic chain (coded for by hisG). Another mechanism of feedback inhibition of ATP-PRTase has been disclosed in Lactococcus lactis where HisG interacts with HisZ, which mediates the feedback inhibition. We analyzed the phylogenetic distribution of the two types of regulation mechanisms. The evolutionary model that we propose predicts that: i) histidine biosynthesis was assembled before the appearance of LUCA; ii) the ancestral his genes were monofunctional and involved in different metabolic pathways, and iii) they underwent differential elongation, duplication and fusion events in different phylogenetic lineages; iv) some of his genes were operonally organized and other scattered in genome; v) they underwent different organization rearrangements during evolution.

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