Heredity (2005) 94, 278–279

www.nature.com/hdy

NEWS AND COMMENTARY

Ecological genetics

The decline and fall of a metabolic pathway in yeast

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Heredity (2005) **94,** 278–279. doi:10.1038/sj.hdy.6800632
Published online 15 December 2004

A commentary on Hittinger CT, Rokas A, Carroll SB (2004). Parallel inactivation of multiple *GAL* pathway genes and ecological diversification in yeasts. *Proc Natl Acad Sci USA* **101:** 14144–14149.

The evolutionary loss of redundant metabolic pathways is little understood compared with the gaining of new adaptive pathways. A recently published study begins to unravel the processes involved in a yeast species.

Yeasts have evolved an incredible diversity of metabolic pathways that are capable of converting a wide array of carbon compounds into energy (Barnett *et al*, 1990). How can we account for the evolution of this diversity? Simple evolutionary principles suggest that the metabolic capabilities of a microbe should evolve in response to the availability of different resources in the environment: new pathways are expected to evolve when novel resources are encountered and existing pathways are expected to degrade in environments that lack the substrate the pathway degrades (Kassen, 2002). Laboratory selection experiments that have tracked the evolution of microbial metabolism in simple, defined environments have lent credence to this theory (Mortlock, 1984; Cooper and Lenski, 2000), but similar studies have not been carried out to investigate the evolution of microbial metabolism in nature. In a recent study, Hittinger *et al* (2004) employ a phylogenetic approach to study the evolution of a well-characterized metabolic pathway, the Leloir pathway for galactose degradation, in a well-known group of microorganisms, the yeasts. The results of this study provide novel and valuable insights into the evolution of metabolic and ecological diversity in a fascinating group of organisms.

The Leloir pathway (*GAL*) is made up of a series of genes that code for structural proteins that transport and degrade the sugar galactose and regulatory proteins that modulate the expression of the *GAL* pathway in response to galactose availability. Despite the ubiquity of this pathway in all domains of life, some species of yeast are unable to degrade galactose, suggesting the existence of genetic variation in the *GAL* pathway among yeast species. To investigate the evolution of galactose metabolism, the authors mapped the ability to degrade galactose onto a well-supported phylogeny of 11 yeast species, seven of which are able to degrade galactose and four of which are unable to. This phylogenetic analysis provides convincing evidence that the common ancestor of all of these species was able to degrade galactose, and that the inability to degrade galactose has evolved on at least three (and possibly four) independent occasions. To investigate the genetic basis of variation in galactose utilization, the authors compared the sequences of all seven *GAL* genes from all 11 species of yeast. Species that can utilize galactose contain a common set of conserved *GAL* genes that are predicted to code for functional, structural and regulatory proteins. Three of the four yeast species that are unable to degrade galactose essentially lack any trace of *GAL* genes. The remaining species, *Saccharomyces kudriavzevii*, contains the visible genetic signature of an intact *GAL* pathway. However, each *GAL* gene exists as a pseudogene that contains numerous stop codons, deletions, and frameshift mutations, implying that *GAL* pathway genes from this species do not code for functional proteins.

How can we explain the multiple independent instances of degeneration of the *GAL* pathway during the diversification of yeast? When a species adapts to a novel set of environmental conditions, or niche, unused structures and functions are expected to degenerate as a cost of adaptation. Two population genetic processes can generate such costs of adaptation. Firstly, antagonistic pleiotropy contributes to the cost of adaptation when mutations that increase fitness in a novel niche cause a degeneration of unused pathways. In this scenario, metabolic pathways degenerate as a direct cause of adaptation to a new niche. Secondly, mutation accumulation occurs when mutations that decay unused functions stochastically accumulate during adaptation to a new niche as a result of genetic drift. In this scenario, unused metabolic pathways degenerate as an indirect consequence of adaptation to a new niche. Although the results of this paper clearly demonstrate that ecological diversification in yeast was associated with costs whose genetic basis can be precisely identified, the authors are unable to infer the population genetic processes (ie pleiotropy or drift) that were responsible for the decay of the *GAL* pathway. This limitation cannot be considered a serious flaw of the study, because even laboratory selection experiments carried out under tightly controlled conditions have had difficulty identifying the population genetic processes that result in the loss of metabolic pathways (Cooper and Lenski, 2000; MacLean and Bell, 2002).

Both theoretical (Horowitz, 1945) and empirical (Mortlock, 1984) studies of metabolic pathway evolution have tended to concentrate on the mechanisms that give rise to new metabolic pathways with novel functions, and not on the degradation of existing pathways. Hittinger and co-workers propose a model for pathway degeneration in which enzymatic steps are lost in the forward order of the pathway and genes that interact with other pathways are least likely to degenerate. Although the authors were unable to find any evidence to support this model using the limited data set analyzed in this paper, more extensive studies using similar methodologies will be able to test this model in a more rigorous manner.

One final aspect of this research that deserves special comment is the fact that Hittinger and co-workers used a large amount of sequence data to construct a well-supported phylogeny of a group of closely related yeast species and to determine the genetic basis of variation in galactose utilization. This work provides an elegant illustration of how the large quantities of sequence data that are now publicly available to researchers can be used to investigate fundamental questions in evolutionary genetics in a powerful manner. Subsequent studies using the approach developed in this paper could provide data that sheds new light on the evolution of microbial metabolic diversity.

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