

On the local regulation of aminoacyl-tRNA synthetases and amino acid biosynthetic enzymes in *Escherichia coli*

Emmeli Taberman
Dept. of Cell and Molecular Biology Uppsala
University
BMC, Box 596
S-75421 Uppsala, Sweden
Emmeli.Taberman@icm.uu.se

Måns Ehrenberg
Dept. of Cell and Molecular Biology Uppsala
University
BMC, Box 596
S-75421 Uppsala, Sweden
Ehrenberg@xray.bmc.uu.se

ABSTRACT

One of the fundamental processes in the bacterial cell is the protein synthesis carried out by ribosomes programmed with messenger RNAs. It is vital for fast growth and high fitness that the supply of amino acids matches the demand raised by protein synthesis. It is also important that transfer RNAs are fully charged with amino acids before they enter the ribosome. The charging reaction is carried out by the twentyone aminoacyl-tRNA synthetases (RS) in the cell. The regulation of the expression of the amino acid synthesising enzymes is known in detail at the molecular level, while there are only a few synthetases that have known local feedback control for their synthesis. Two of these are threonyl-RS and phenylalanyl-RS, which are controlled by an autogenous feedback control at the translational level and ribosome mediated attenuation of transcription respectively [1]. The amino acid synthetic enzymes are typically controlled at the transcriptional level, either by repressor or attenuation mechanisms [2].

We have studied the regulation of the amino acid biosynthetic enzymes and the tRNA synthetases. Of particular interest was the possible interference between control of amino acid biosynthetic operons and genes for tRNA synthetases. In the first step of the analysis we used macroscopic modelling of the metabolic flows and charging of tRNAs in *E.coli*. Interference between the control mechanisms of these two enzyme systems was found both in steady state analysis and simulations of the system's dynamics, and turned out to be innocuous. It was also found in the dynamic simulations that attenuation mechanisms are inferior to repressor and autogenous control systems, confirming

conclusions both from steady state considerations and closely related work by J. Elf et al. [3]. The reason for the inferiority of the attenuation mechanism is that the interval where it can regulate is much smaller than for repressor control. In fact, attenuation control tends to force the cell into a state where the ribosome is partially starved for aminoacyl-tRNA, which directly inhibits growth and increases the error frequency of code translation. This poses an intriguing question: why are attenuation mechanisms ubiquitous in bacteria, if repressor control is so much better? We are now extending the modelling to include global regulatory systems and in particular stringent control by the effector molecule ppGpp. The aim is to determine whether the shortcomings of attenuation of transcription can be overcome by subsidiary, global control mechanisms.

ADDITIONAL AUTHOR

Johan Elf (Dept. of Cell and Molecular Biology, Uppsala University, email address: Johan.Elf@icm.uu.se)

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