



CENTRE OF BIOLOGICAL ENGINEERING
UNIVERSIDADE DO MINHO



INSTITUTE FOR BIOTECHNOLOGY AND BIOENGINEERING

Metabolomic approaches for the characterization of metabolic bottlenecks in recombinant protein production processes

Sónia Carneiro, Eugénio C. Ferreira, Isabel Rocha

IBB-Institute for Biotechnology and Bioengineering, Centre of Biological Engineering, Universidade do Minho, Campus de Gualtar, 4710-057 Braga, Portugal

The optimization of bioprocesses using recombinant microorganisms is still restrained by the lack of information available on the metabolic responses induced by various stress conditions. The rapid exhaustion of essential metabolic precursors (e.g. amino acids) and cellular energy toward recombinant biosynthetic processes may result in the imbalance of the metabolism of the host cell, also called metabolic burden. In the past few years, the association of this metabolic burden with other cellular events, like the stringent response, has been demonstrated [1]. The unusual accumulation of ppGpp, a molecule produced by the ribosome-associated RelA synthetase induced by the deprivation of amino acids, is the hallmark of this stress response that results in the inhibition of cellular growth and lower productivity levels. The regulatory mechanisms of this ppGpp-induced response are known in some detail, but the impact of this response on the cellular metabolism has been less studied. Metabolomic analyses can provide substantial information at the biochemical level, in particular during recombinant bioprocesses. Therefore, metabolomic-based approaches [2], including profiling of intracellular and extracellular metabolite pools, were applied to investigate the influence of recombinant processes on the host cells' metabolism. In these studies two *E. coli* strains (*E. coli* W3110 and the isogenic Δ relA mutant) were used to investigate the advantages of using "relaxed" phenotypes (i.e. Δ relA mutant strain) as host cells in recombinant bioprocesses. Indeed, this cellular system presented major advantages in terms of biomass yield and productivity, which implied a remarkable improvement in recombinant bioprocesses.

References

- [1] Hoffmann F and Rinas U, "Stress induced by recombinant protein production in *Escherichia coli*", *Advances in Biochemical Engineering/Biotechnology* (2004) **89**:73-92.
- [2] K.Saito and F.Matsuda, "Metabolomics for Functional Genomics, Systems Biology, and Biotechnology", *Annual Review of Plant Biology* (2010) **61**:463-489.