Stellingen
Behoren bij het proefschrift

Functional genomics to study protein secretion stress in *Aspergillus niger*

1. The Unfolded protein response (UPR) pathway in fungi has mainly been associated to a pathway triggered by the accumulation of misfolded protein in the ER. The arisen idea of a “physiological UPR” activated in secretory cells different from a “stress UPR” activated by a disturbed ER homeostasis might represent a new UPR paradigm in filamentous fungi.

   *This thesis*

2. Deletion of the *hacA* gene results in a strong phenotypic effect and severely reduced growth indicating that *A. niger* HacA is not only required under ER stress conditions, but also during normal growth conditions.

   *This thesis*


3. Constitutive activation of HacA leads to the down-regulation of the entire AmyR regulon.

   *This thesis*

4. The lack of a strong UPR response in some strains producing low levels of heterologous proteins strongly suggests that also non-UPR mediated bottlenecks exist in *A. niger* that hamper efficient secretion.

   *This thesis*

5. Strain improvements in filamentous fungi have been by a trial-and-error process but it is now becoming more feasible to introduce rationally designed metabolic changes through genetic modification.


6. The biological relevance of the *hacA* 5’UTR truncation in *A. niger* remains mysterious as mutating the 5’splice site did not seem to affect HacA function.


7. Modulating the levels of *hacA* (deletion, overexpression or constitutive activation) does not per definition result in higher production levels of heterologous proteins.


   *This thesis*
8. The synergism between ERAD and UPR pathways in the maintenance of protein quality control in the ER may represent a vulnerability of *Aspergillus sp.* that could be exploited to unravel new antifungal targets and increase the effectiveness of antifungal therapy. 

9. Surprisingly, doing a PhD requires as much inspiration as hard work.

10. Science is a never-ending puzzle to which each scientist contributes with just a few pieces.

11. Europe is relatively small but cultural differences between its countries are rather enormous.