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The role of autophagy during carbon starvation in *Aspergillus niger* Burggraaf, M.A.

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References

- Abramoff, M.D., Magalhães, P.J., and Ram, S.J. (2004) Image processing with ImageJ. *Biophotonics Int* **11**: 36–42.
- Adams, T.H., Wieser, J.K., and Yu, J.H. (1998) Asexual sporulation in *Aspergillus nidulans*. *Microbiol Mol Biol Rev* **62**: 35–54.
- Al-Sheikh, H., Watson, A.J., Lacey, G.A., Punt, P.J., MacKenzie, D.A., Jeenes, D.J., *et al.* (2004) Endoplasmic reticulum stress leads to the selective transcriptional downregulation of the glucoamylase gene in *Aspergillus niger*. *Mol Microbiol* **53**: 1731–1742.
- Amor, C., Domínguez, A.I., Lucas, J.R. De, and Laborda, F. (2000) The catabolite inactivation of *Aspergillus nidulans* isocitrate lyase occurs by specific autophagy of peroxisomes. *Arch Microbiol* **174**: 59–66.
- Andersen, M.R., Giese, M., Vries, R.P. de, and Nielsen, J. (2012) Mapping the polysaccharide degradation potential of *Aspergillus niger*. *BMC Genomics* **13**: 313.
- Andersen, M.R., Salazar, M.P., Schaap, P.J., Vondervoort, P.J.I. van de, Culley, D., Thykaer, J., *et al.* (2011) Comparative genomics of citric-acid-producing *Aspergillus niger* ATCC 1015 versus enzyme-producing CBS 513.88. *Genome Res* **21**: 885–897.
- Archer, D.B. (2000) Filamentous fungi as microbial cell factories for food use. *Curr Opin Biotechnol* **11**: 478–483.
- Arentshorst, M., Lagendijk, E.L., and Ram, A.F. (2015a) A new vector for efficient gene targeting to the *pyrG* locus in *Aspergillus niger*. *Fungal Biol Biotechnol* **2**: 2.
- Arentshorst, M., Niu, J., and Ram, A.F.J. (2015b) Efficient generation of *Aspergillus niger* knock out strains by combining NHEJ mutants and a split marker approach. In *Genetic Transformation Systems in Fungi*. Berg, M.A. van den, and Maruthachalam, K. (eds). Cham (Switzerland): Springer International Publishing pp. 263–272.
- Arentshorst, M., Ram, A.F.J., and Meyer, V. (2012) Using non-homologous end-joining-deficient strains for functional gene analyses in filamentous fungi. In *Methods in Molecular Biology*. Bolton, M.D., and Thomma, B.P.H.J. (eds). New York: Humana Press pp. 133–150.
- Atoui, A., Kastner, C., Larey, C.M., Thokala, R., Etxebeste, O., Espeso, E.A., *et al.* (2010) Cross-talk between light and glucose regulation controls toxin production and morphogenesis in *Aspergillus nidulans*. *Fungal Genet Biol* **47**: 962–72.
- Bai, Z., Harvey, L.M., and McNeil, B. (2003) Oxidative stress in submerged cultures of fungi. *Crit Rev Biotechnol* **23**: 267–302.
- Bartoszewska, M., and Kiel, J.A.K.W. (2011) The role of macroautophagy in development of filamentous fungi. *Antioxid Redox Signal* **14**: 2271–2287.
- Bartoszewska, M., Kiel, J.A.K.W., Bovenberg, R.A.L., Veenhuis, M., and Klei, I.J. van der (2011) Autophagy Deficiency Promotes β -Lactam Production in *Penicillium chrysogenum*. *Appl Environ Microbiol* **77**: 1413–1422.

- Bauer, S., Vasu, P., Persson, S., Mort, A.J., and Somerville, C.R. (2006) Development and application of a suite of polysaccharide-degrading enzymes for analyzing plant cell walls. *Proc Natl Acad Sci U S A* **103**: 11417–22.
- Bayram, O., and Braus, G.H. (2012) Coordination of secondary metabolism and development in fungi: the velvet family of regulatory proteins. *FEMS Microbiol Rev* **36**: 1–24.
- Bennett, J.W., and Lasure, L.L. (1991) *More Gene Manipulations in Fungi*. San Diego, CA: Academic Press.
- Benson, G. (1999) Tandem repeats finder: a program to analyze DNA sequences. *Nucleic Acids Res* **27**: 573–80.
- Benz, J.P., Chau, B.H., Zheng, D., Bauer, S., Glass, N.L., and Somerville, C.R. (2014) A comparative systems analysis of polysaccharide-elicited responses in *Neurospora crassa* reveals carbon source-specific cellular adaptations. *Mol Microbiol* **91**: 275–99.
- Bernardo, S.M.H., Gray, K.-A., Todd, R.B., Cheetham, B.F., and Katz, M.E. (2007) Characterization of regulatory non-catalytic hexokinases in *Aspergillus nidulans*. *Mol Genet Genomics* **277**: 519–32.
- Bleichrodt, R.-J., Hulsman, M., Wösten, H.A.B., and Reinders, M.J.T. (2015) Switching from a unicellular to multicellular organization in an *Aspergillus niger* hypha. *MBio* **6**: e00111-15.
- Bos, C.J., Debets, A.J., Swart, K., Huybers, A., Kobus, G., and Slakhorst, S.M. (1988) Genetic analysis and the construction of master strains for assignment of genes to six linkage groups in *Aspergillus niger*. *Curr Genet* **14**: 437–443.
- Braaksma, M., Martens-Uzunova, E.S., Punt, P.J., and Schaap, P.J. (2010) An inventory of the *Aspergillus niger* secretome by combining in silico predictions with shotgun proteomics data. *BMC Genomics* **11**: 584–594.
- Braaksma, M., Smilde, A.K., Werf, M.J. van der, and Punt, P.J. (2009) The effect of environmental conditions on extracellular protease activity in controlled fermentations of *Aspergillus niger*. *Microbiology* **155**: 3430–3439.
- Brakhage, A.A., Spröte, P., Al-Abdallah, Q., Gehrke, A., Plattner, H., and Tüncher, A. (2004) Regulation of penicillin biosynthesis in filamentous fungi. *Adv Biochem Eng Biotechnol* **88**: 45–90.
- Brown, N.A., Gouvea, P.F. de, Krohn, N.G., Savoldi, M., and Goldman, G.H. (2013) Functional characterisation of the non-essential protein kinases and phosphatases regulating *Aspergillus nidulans* hydrolytic enzyme production. *Biotechnol Biofuels* **6**: 91.
- Bruns, C., McCaffery, J.M., Curwin, A.J., Duran, J.M., and Malhotra, V. (2011) Biogenesis of a novel compartment for autophagosome-mediated unconventional protein secretion. *J Cell Biol* **195**: 979–992.
- Burggraaf, A.-M., Punt, P.J., and Ram, A.F.J. (2016) The unconventional secretion of PepN is independent of a functional autophagy machinery in the filamentous fungus *Aspergillus niger*. *FEMS Microbiol Lett* **363**: fnw152.
- Burggraaf, A.-M., and Ram, A.F.J. (2016) Autophagy is dispensable to overcome ER stress in the filamentous fungus *Aspergillus niger*. *Microbiologyopen* **5**: 647–658.

- Carvalho, N.D.S.P., Arentshorst, M., Jin Kwon, M., Meyer, V., and Ram, A.F.J. (2010) Expanding the ku70 toolbox for filamentous fungi: establishment of complementation vectors and recipient strains for advanced gene analyses. *Appl Microbiol Biotechnol* **87**: 1463–1473.
- Carvalho, N.D.S.P., Arentshorst, M., Kooistra, R., Stam, H., Sagt, C.M., Hondel, C.A.M.J.J. van den, and Ram, A.F.J. (2011a) Effects of a defective ERAD pathway on growth and heterologous protein production in *Aspergillus niger*. *Appl Microbiol Biotechnol* **89**: 357–373.
- Carvalho, N.D.S.P., Arentshorst, M., Weenink, X.O., Punt, P.J., Hondel, C.A.M.J.J. van den, and Ram, A.F.J. (2011b) Functional YFP-tagging of the essential GDP-mannose transporter reveals an important role for the secretion related small GTPase SrgC protein in maintenance of Golgi bodies in *Aspergillus niger*. *Fungal Biol* **115**: 253–264.
- Carvalho, N.D.S.P., Jørgensen, T.R., Arentshorst, M., Nitsche, B.M., Hondel, C.A.M.J.J. van den, Archer, D.B., and Ram, A.F.J. (2012) Genome-wide expression analysis upon constitutive activation of the HacA bZIP transcription factor in *Aspergillus niger* reveals a coordinated cellular response to counteract ER stress. *BMC Genomics* **13**: 350–366.
- Cheng, Y. (2011) Survival and death of endoplasmic-reticulum-stressed cells: Role of autophagy. *World J Biol Chem* **2**: 226–231.
- Cheong, H., Nair, U., Geng, J., and Klionsky, D.J. (2008) The Atg1 kinase complex is involved in the regulation of protein recruitment to initiate sequestering vesicle formation for nonspecific autophagy in *Saccharomyces cerevisiae*. *Mol Biol Cell* **19**: 668–681.
- Cheong, H., Yorimitsu, T., Reggiori, F., Legakis, J.E., Wang, C.-W., and Klionsky, D.J. (2005) Atg17 Regulates the Magnitude of the Autophagic Response. *Mol Biol Cell* **16**: 3438–3453.
- Choi, C.-J., Ju, H.-J., Park, B.-H., Qin, R., Jahng, K.-Y., Han, D.-M., and Chae, K.-S. (2005) Isolation and characterization of the *Aspergillus nidulans* egIC gene encoding a putative beta-1,3-endoglucanase. *Fungal Genet Biol* **42**: 590–600.
- Ciechanover, A., and Kwon, Y.T. (2017) Protein Quality Control by Molecular Chaperones in Neurodegeneration. *Front Neurosci* **11**: 185.
- Codogno, P., and Meijer, A.J. (2005) Autophagy and signaling: Their role in cell survival and cell death. *Cell Death Differ* **12**: 1509–1518.
- Coradetti, S.T., Craig, J.P., Xiong, Y., Shock, T., Tian, C., and Glass, N.L. (2012) Conserved and essential transcription factors for cellulase gene expression in ascomycete fungi. *Proc Natl Acad Sci U S A* **109**: 7397–402.
- Cubero, B., and Scazzocchio, C. (1994) Two different, adjacent and divergent zinc finger binding sites are necessary for CREA-mediated carbon catabolite repression in the proline gene cluster of *Aspergillus nidulans*. *EMBO J* **13**: 407–15.
- Dechant, R., and Peter, M. (2008) Nutrient signals driving cell growth. *Curr Opin Cell Biol* **20**: 678–687.
- Deegan, S., Saveljeva, S., Gorman, A.M., and Samali, A. (2013) Stress-induced self-cannibalism: On the regulation of autophagy by endoplasmic reticulum stress. *Cell Mol Life Sci* **70**: 2425–2441.
- Delmas, S., Pullan, S.T., Gaddipati, S., Kokolski, M., Malla, S., Blythe, M.J., et al. (2012) Uncovering the genome-wide transcriptional responses of the filamentous fungus *Aspergillus niger* to lignocellulose using RNA sequencing. *PLoS Genet* **8**: e1002875.

- Deng, Y.Z., and Naqvi, N.I. (2010) A vacuolar glucoamylase, Sga1, participates in glycogen autophagy for proper asexual differentiation in *Magnaporthe oryzae*. *Autophagy* **6**: 455–461.
- Ditch, S., and Paull, T.T. (2012) The ATM protein kinase and cellular redox signaling: beyond the DNA damage response. *Trends Biochem Sci* **37**: 15–22.
- Dupont, N., Jiang, S., Pilli, M., Ornatowski, W., Bhattacharya, D., and Deretic, V. (2011) Autophagy-based unconventional secretory pathway for extracellular delivery of IL-1 β . *EMBO J* **30**: 4701–4711.
- Duran, J.M., Anjard, C., Stefan, C., Loomis, W.F., and Malhotra, V. (2010) Unconventional secretion of Acb1 is mediated by autophagosomes. *J Cell Biol* **188**: 527–536.
- Dyavaiah, M., Rooney, J.P., Chittur, S.V., Lin, Q., and Begley, T.J. (2011) Autophagy-dependent regulation of the DNA damage response protein ribonucleotide reductase 1. *Mol Cancer Res* **9**: 462–475.
- Dyer, P.S., Ingram, D.S., and Johnstone, K. (1992) The control of sexual morphogenesis in the Ascomycotina. *Biol Rev* **67**: 421–458.
- Dyer, P.S., and O’Gorman, C.M. (2012) Sexual development and cryptic sexuality in fungi: insights from *Aspergillus* species. *FEMS Microbiol Rev* **36**: 165–92.
- Ellström, M., Shah, F., Johansson, T., Åhrén, D., Persson, P., and Tunlid, A. (2015) The carbon starvation response of the ectomycorrhizal fungus *Paxillus involutus*. *FEMS Microbiol Ecol* **91**: fiv027.
- Emri, T., Molnár, Z., Pusztahelyi, T., and Pócsi, I. (2004) Physiological and morphological changes in autolyzing *Aspergillus nidulans* cultures. *Folia Microbiol (Praha)* **49**: 277–84.
- Emri, T., Molnár, Z., Pusztahelyi, T., Varcza, Z., and Pócsi, I. (2005) The fluG-BrlA pathway contributes to the initialisation of autolysis in submerged *Aspergillus nidulans* cultures. *Mycol Res* **109**: 757–63.
- Emri, T., Molnár, Z., Szilágyi, M., and Pócsi, I. (2008) Regulation of autolysis in *Aspergillus nidulans*. *Appl Biochem Biotechnol* **151**: 211–220.
- Emri, T., Molnár, Z., Veres, T., Pusztahelyi, T., Dudás, G., and Pócsi, I. (2006) Glucose-mediated repression of autolysis and conidiogenesis in *Emericella nidulans*. *Mycol Res* **110**: 1172–8.
- Emri, T., Szilágyi, M., László, K., M-Hamvas, M., and Pócsi, I. (2009) PepJ is a new extracellular proteinase of *Aspergillus nidulans*. *Folia Microbiol (Praha)* **54**: 105–9.
- Erdei, E., Pusztahelyi, T., Miskei, M., Barna, T., and Pócsi, I. (2008) Characterization and heterologous expression of an age-dependent fungal/bacterial type chitinase of *Aspergillus nidulans*. *Acta Microbiol Immunol Hung* **55**: 351–361.
- Escott, G.M., Hearn, V.M., and Adams, D.J. (1998) Inducible chitinolytic system of *Aspergillus fumigatus*. *Microbiology* **144**: 1575–1581.
- Etxebeeste, O., Garzia, A., Espeso, E.A., and Ugalde, U. (2010) *Aspergillus nidulans* asexual development: making the most of cellular modules. *Trends Microbiol* **18**: 569–76.
- Evangelinos, M., Martzoukou, O., Chorozián, K., Amillis, S., and Diállinas, G. (2016) BsdA^{Bsd2}-dependent vacuolar turnover of a misfolded version of the UapA transporter along the secretory pathway: prominent role of selective autophagy. *Mol Microbiol* **100**: 893–911.
- Falcone, C., and Mazzoni, C. (2016) External and internal triggers of cell death in yeast. *Cell Mol Life Sci* **73**: 2237–2250.
- Feng, Y., He, D., Yao, Z., and Klionsky, D.J. (2014) The machinery of macroautophagy. *Cell Res* **24**: 24–41.

- Fernandes, P.N., Mannarino, S.C., Silva, C.G., Pereira, M.D., Panek, A.D., and Eleutherio, E.C.A. (2007) Oxidative stress response in eukaryotes: effect of glutathione, superoxide dismutase and catalase on adaptation to peroxide and menadione stresses in *Saccharomyces cerevisiae*. *Redox Rep* **12**: 236–244.
- Flipphi, M., Vondervoort, P.J.I. van de, Ruijter, G.J.G., Visser, J., Arst, H.N., and Felenbok, B. (2003) Onset of carbon catabolite repression in *Aspergillus nidulans*: Parallel involvement of hexokinase and glucokinase in sugar signaling. *J Biol Chem* **278**: 11849–57.
- Fontaine, T., Hartland, R.P., Beauvais, A., Diaquin, M., and Latge, J.P. (1997) Purification and characterization of an endo-1,3-beta-glucanase from *Aspergillus fumigatus*. *Eur J Biochem* **243**: 315–321.
- Foreman, P.K., Brown, D., Dankmeyer, L., Dean, R., Diener, S., Dunn-Coleman, N.S., et al. (2003) Transcriptional regulation of biomass-degrading enzymes in the filamentous fungus *Trichoderma reesei*. *J Biol Chem* **278**: 31988–97.
- Fujioka, T., Mizutani, O., Furukawa, K., Sato, N., Yoshimi, A., Yamagata, Y., et al. (2007) MpkA-Dependent and -independent cell wall integrity signaling in *Aspergillus nidulans*. *Eukaryot Cell* **6**: 1497–510.
- Fujita, E., Kouroku, Y., Isoai, A., Kumagai, H., Misutani, A., Matsuda, C., et al. (2007) Two endoplasmic reticulum-associated degradation (ERAD) systems for the novel variant of the mutant dysferlin: Ubiquitin/proteasome ERAD(I) and autophagy/lysosome ERAD(II). *Hum Mol Genet* **16**: 618–629.
- Fujiwara, M., Ichinomiya, M., Motoyama, T., Horiuchi, H., Ohta, A., and Takagi, M. (2000) Evidence that the *Aspergillus nidulans* class I and class II chitin synthase genes, chsC and chsA, share critical roles in hyphal wall integrity and conidiophore development. *J Biochem* **127**: 359–366.
- Glass, N.L., Schmoll, M., Cate, J.H.D., and Coradetti, S. (2013) Plant cell wall deconstruction by ascomycete fungi. *Annu Rev Microbiol* **67**: 477–98.
- Gordon, C.L., Khalaj, V., Ram, A.F.J., Archer, D.B., Brookman, J.L., Trinci, A.P.J., et al. (2000) Glucoamylase::green fluorescent protein fusions to monitor protein secretion in *Aspergillus niger*. *Microbiology* **146**: 415–426.
- Groot, P.W.J. De, Ram, A.F., and Klis, F.M. (2005) Features and functions of covalently linked proteins in fungal cell walls. *Fungal Genet Biol* **42**: 657–75.
- Guillemette, T., Peij, N.N. van, Goosen, T., Lanthaler, K., Robson, G.D., Hondel, C.A. van den, et al. (2007) Genomic analysis of the secretion stress response in the enzyme-producing cell factory *Aspergillus niger*. *BMC Genomics* **8**: 158.
- Ha, J., Guan, K.L., and Kim, J. (2015) AMPK and autophagy in glucose/glycogen metabolism. *Mol Aspects Med* **46**: 46–62.
- Han, K., Lee, D., Kim, J., Kim, M., Kim, W., Park, Y., et al. (2003) Environmental factors affecting development of *Aspergillus nidulans*. *J Microbiol* **41**: 34–40.
- Hartingsveldt, W. van, Mattern, I.E., Zeijl, C.M. van, Pouwels, P.H., and Hondel, C.A. van den (1987) Development of a homologous transformation system for *Aspergillus niger* based on the pyrG gene. *Mol Gen Genet* **206**: 71–75.
- Hartl, L., Gastebois, A., Amanianda, V., and Latgé, J.-P. (2011) Characterization of the GPI-anchored endo β -1,3-glucanase Eng2 of *Aspergillus fumigatus*. *Fungal Genet Biol* **48**: 185–91.

- Heimel, K. (2015) Unfolded protein response in filamentous fungi—implications in biotechnology. *Appl Microbiol Biotechnol* **99**: 121–132.
- Homberg, J.P. van den, Vondervoort, P.J. van de, Fraissinet-Tachet, L., and Visser, J. (1997a) *Aspergillus* as a host for heterologous protein production: the problem of proteases. *Trends Biotechnol* **15**: 256–263.
- Homberg, J.P.T.W. van den, Sollewijn Gelpke, M.D., Vondervoort, P.J.I. van de, Buxton, F.P., and Visser, J. (1997b) Disruption of three acid proteases in *Aspergillus niger*—effects on protease spectrum, intracellular proteolysis, and degradation of target proteins. *Eur J Biochem* **247**: 605–613.
- Horiuchi, H. (2009) Functional diversity of chitin synthases of *Aspergillus nidulans* in hyphal growth, conidiophore development and septum formation. *Med Mycol* **47 Suppl 1**: S47–52.
- Inoue, Y., and Klionsky, D.J. (2010) Regulation of macroautophagy in *Saccharomyces cerevisiae*. *Semin Cell Dev Biol* **21**: 664–670.
- Ishida, Y., Yamamoto, A., Kitamura, A., Lamandé, S.R., Yoshimori, T., Bateman, J.F., et al. (2009) Autophagic elimination of misfolded procollagen aggregates in the endoplasmic reticulum as a means of cell protection. *Mol Biol Cell* **20**: 2744–2754.
- Ishihama, Y., Oda, Y., Tabata, T., Sato, T., Nagasu, T., Rappsilber, J., and Mann, M. (2005) Exponentially modified protein abundance index (emPAI) for estimation of absolute protein amount in proteomics by the number of sequenced peptides per protein. *Mol Cell Proteomics* **4**: 1265–72.
- Jacobs, D.I., Olsthoorn, M.M.A., Maillet, I., Akeroyd, M., Breestraat, S., Donkers, S., et al. (2009) Effective lead selection for improved protein production in *Aspergillus niger* based on integrated genomics. *Fungal Genet Biol* **46**: S141–S152.
- Jamieson, D.J. (1992) *Saccharomyces cerevisiae* has distinct adaptive responses to both hydrogen peroxide and menadione. *J Bacteriol* **174**: 6678–6681.
- Jaques, A.K., Fukamizo, T., Hall, D., Barton, R.C., Escott, G.M., Parkinson, T., et al. (2003) Disruption of the gene encoding the ChiB1 chitinase of *Aspergillus fumigatus* and characterization of a recombinant gene product. *Microbiology* **149**: 2931–2939.
- Jaroszuk-Scisel, J., Kurek, E., Slomka, A., Janczarek, M., and Rodzik, B. Activities of cell wall degrading enzymes in autolyzing cultures of three *Fusarium culmorum* isolates: growth-promoting, deleterious and pathogenic to rye (*Secale cereale*). *Mycologia* **103**: 929–45.
- Jørgensen, T.R., Nitsche, B.M., Lamers, G.E., Arentshorst, M., Hondel, C.A. van den, and Ram, A.F. (2010) Transcriptomic insights into the physiology of *Aspergillus niger* approaching a specific growth rate of zero. *Appl Environ Microbiol* **76**: 5344–5355.
- Kabeya, Y., Kamada, Y., Baba, M., Takikawa, H., Sasaki, M., and Ohsumi, Y. (2005) Atg17 Functions in Cooperation with Atg1 and Atg13 in Yeast Autophagy. *Mol Biol Cell* **16**: 2544–2553.
- Kageyama, T. (2002) Pepsinogens, progastricsins, and prochymosins: structure, function, evolution, and development. *Cell Mol Life Sci* **59**: 288–306.
- Kamada, Y., Funakoshi, T., Shintani, T., Nagano, K., Ohsumi, M., and Ohsumi, Y. (2000) Tor-mediated induction of autophagy via an Apg1 protein kinase complex. *J Cell Biol* **150**: 1507–1513.

- Kamimoto, T., Shoji, S., Hidvegi, T., Mizushima, N., Umabayashi, K., Perlmutter, D.H., and Yoshimori, T. (2006) Intracellular inclusions containing mutant α 1-antitrypsin Z are propagated in the absence of autophagic activity. *J Biol Chem* **281**: 4467–4476.
- Kang, J.Y., Chun, J., Jun, S.-C., Han, D.-M., Chae, K.-S., and Jahng, K.Y. (2013) The MpkB MAP kinase plays a role in autolysis and conidiation of *Aspergillus nidulans*. *Fungal Genet Biol* **61**: 42–9.
- Kanki, T., Furukawa, K., and Yamashita, S. ichi (2015) Mitophagy in yeast: Molecular mechanisms and physiological role. *Biochim Biophys Acta–Mol Cell Res* **1853**: 2756–2765.
- Kanki, T., Klionsky, D.J., and Okamoto, K. (2011) Mitochondria autophagy in yeast. *Antioxidants Redox Signal* **14**: 1989–2001.
- Kasuga, T., and Glass, N.L. (2008) Dissecting colony development of *Neurospora crassa* using mRNA profiling and comparative genomics approaches. *Eukaryot Cell* **7**: 1549–64.
- Katz, M.E., Bernardo, S.M., and Cheetham, B.F. (2008) The interaction of induction, repression and starvation in the regulation of extracellular proteases in *Aspergillus nidulans*: evidence for a role for CreA in the response to carbon starvation. *Curr Genet* **54**: 47–55.
- Katz, M.E., Braunberger, K., Yi, G., Cooper, S., Nonhebel, H.M., and Gondro, C. (2013) A p53-like transcription factor similar to Ndt80 controls the response to nutrient stress in the filamentous fungus, *Aspergillus nidulans*. *F1000Research* **2**: 72.
- Katz, M.E., Flynn, P.K., VanKuyk, P.A., and Cheetham, B.F. (1996) Mutations affecting extracellular protease production in the filamentous fungus *Aspergillus nidulans*. *Mol Gen Genet* **250**: 715–24.
- Katz, M.E., Gray, K.-A., and Cheetham, B.F. (2006) The *Aspergillus nidulans* xprG (phoG) gene encodes a putative transcriptional activator involved in the response to nutrient limitation. *Fungal Genet Biol* **43**: 190–9.
- Katz, M.E., Rice, R.N., and Cheetham, B.F. (1994) Isolation and characterization of an *Aspergillus nidulans* gene encoding an alkaline protease. *Gene* **150**: 287–92.
- Kautto, L., Grinyer, J., Paulsen, I., Tetu, S., Pillai, A., Pardiwalla, S., et al. (2013) Stress effects caused by the expression of a mutant cellobiohydrolase I and proteasome inhibition in *Trichoderma reesei* Rut-C30. *N Biotechnol* **30**: 183–191.
- Kelly, R., Register, E., Hsu, M.J., Kurtz, M., and Nielsen, J. (1996) Isolation of a gene involved in 1,3-beta-glucan synthesis in *Aspergillus nidulans* and purification of the corresponding protein. *J Bacteriol* **178**: 4381–91.
- Khaminets, A., Heinrich, T., Mari, M., Grumati, P., Huebner, A.K., Akutsu, M., et al. (2015) Regulation of endoplasmic reticulum turnover by selective autophagy. *Nature* **522**: 354–358.
- Kielbasa, S.M., Wan, R., Sato, K., Horton, P., and Frith, M.C. (2011) Adaptive seeds tame genomic sequence comparison. *Genome Res* **21**: 487–93.
- Kikuma, T., and Kitamoto, K. (2011) Analysis of autophagy in *Aspergillus oryzae* by disruption of Aogat13, Aogat4, and Aogat15 genes. *FEMS Microbiol Lett* **316**: 61–69.
- Kikuma, T., Mitani, T., Kohara, T., Maruyama, J. ichi, and Kitamoto, K. (2017a) Carbon and nitrogen depletion-induced nucleophagy and selective autophagic sequestration of a whole nucleus in multinucleate cells of the filamentous fungus *Aspergillus oryzae*. *J Gen Appl Microbiol* **63**: 139–146.

- Kikuma, T., Ohneda, M., Arioka, M., and Kitamoto, K. (2006) Functional analysis of the ATG8 homologue Aogatg8 and role of autophagy in differentiation and germination in *Aspergillus oryzae*. *Eukaryot Cell* **5**: 1328–1336.
- Kikuma, T., Tadokoro, T., Maruyama, J., and Kitamoto, K. (2017b) AoAtg26, a putative sterol glucosyltransferase, is required for autophagic degradation of peroxisomes, mitochondria, and nuclei in the filamentous fungus *Aspergillus oryzae*. *Biosci Biotechnol Biochem* **81**: 384–395.
- Kim, S., Matsuo, I., Ajisaka, K., Nakajima, H., and Kitamoto, K. (2002) Cloning and characterization of the nagA gene that encodes beta-n-acetylglucosaminidase from *Aspergillus nidulans* and its expression in *Aspergillus oryzae*. *Biosci Biotechnol Biochem* **66**: 2168–75.
- Kimura, S., Maruyama, J.I., Kikuma, T., Arioka, M., and Kitamoto, K. (2011) Autophagy delivers misfolded secretory proteins accumulated in endoplasmic reticulum to vacuoles in the filamentous fungus *Aspergillus oryzae*. *Biochem Biophys Res Commun* **406**: 464–470.
- Kineth, M.A., Anjard, C., Fuller, D., Guizzunti, G., Loomis, W.F., and Malhotra, V. (2007) The Golgi-associated protein GRASP is required for unconventional protein secretion during development. *Cell* **130**: 524–34.
- Klarmund, J., Bender, K., and Luke, B. (2014) High nutrient levels and TORC1 activity reduce cell viability following prolonged telomere dysfunction and cell cycle arrest. *Cell Rep* **9**: 324–335.
- Kourouki, Y., Fujita, E., Tanida, I., Ueno, T., Isoai, A., Kumagai, H., *et al.* (2007) ER stress (PERK/eIF2alpha phosphorylation) mediates the polyglutamine-induced LC3 conversion, an essential step for autophagy formation. *Cell Death Differ* **14**: 230–239.
- Kraft, C., Reggiori, F., and Peter, M. (2009) Selective types of autophagy in yeast. *Biochim Biophys Acta–Mol Cell Res* **1793**: 1404–1412.
- Krijgsheld, P., Altelaar, A.F.M., Post, H., Ringrose, J.H., Müller, W.H., Heck, A.J.R., and Wösten, H.A.B. (2012) Spatially resolving the secretome within the mycelium of the cell factory *Aspergillus niger*. *J Proteome Res* **11**: 2807–18.
- Krijgsheld, P., Nitsche, B.M., Post, H., Levin, A.M., Müller, W.H., Heck, A.J.R., *et al.* (2013) Deletion of flbA results in increased secretome complexity and reduced secretion heterogeneity in colonies of *Aspergillus niger*. *J Proteome Res* **12**: 1808–19.
- Krishnan, K., Feng, X., Powers-Fletcher, M. V., Bick, G., Richie, D.L., Woollett, L. a., and Askew, D.S. (2013) Effects of a defective endoplasmic reticulum-associated degradation pathway on the stress response, virulence, and antifungal drug susceptibility of the mold pathogen *Aspergillus fumigatus*. *Eukaryot Cell* **12**: 512–519.
- Krohn, N.G., Brown, N.A., Colabardini, A.C., Reis, T., Savoldi, M., Dinamarco, T.M., *et al.* (2014) The *Aspergillus nidulans* ATM kinase regulates mitochondrial function, glucose uptake and the carbon starvation response. *G3 (Bethesda)* **4**: 49–62.
- Kruse, K.B., Dear, A., Kaltenbrun, E.R., Crum, B.E., George, P.M., Brennan, S.O., and McCracken, A. a (2006) Mutant fibrinogen cleared from the endoplasmic reticulum via endoplasmic reticulum-associated protein degradation and autophagy: an explanation for liver disease. *Am J Pathol* **168**: 1299–1308.

- Kuma, A., Hatano, M., Matsui, M., Yamamoto, A., Nakaya, H., Yoshimori, T., *et al.* (2004) The role of autophagy during the early neonatal starvation period. *Nature* **432**: 1032–1036.
- Kuo, M.J., and Alexander, M. (1967) Inhibition of the lysis of fungi by melanins. *J Bacteriol* **94**: 624–9.
- Kwon, H.S., Kawaguchi, K., Kikuma, T., Takegawa, K., Kitamoto, K., and Higuchi, Y. (2017) Analysis of an acyl-CoA binding protein in *Aspergillus oryzae* that undergoes unconventional secretion. *Biochem Biophys Res Commun* **493**: 481–486.
- Lagopodi, A.L., Ram, A.F.J., Lamers, G.E.M., Punt, P.J., Hondel, C.A.M.J.J. Van den, Lugtenberg, B.J.J., and Bloemberg, G. V. (2002) Novel aspects of tomato root colonization and infection by *Fusarium oxysporum* f. sp. *radicis-lycopersici* Revealed by confocal laser scanning microscopic analysis using the green fluorescent protein as a marker. *Mol Plant-Microbe Interact* **15**: 172–179.
- Lahoz, R., Reyes, F., and Perez Leblic, M.I. (1976) Lytic enzymes in the autolysis of filamentous fungi. *Mycopathologia* **60**: 45–9.
- Latgé, J.-P. (2007) The cell wall: a carbohydrate armour for the fungal cell. *Mol Microbiol* **66**: 279–90.
- Latgé, J.P., Mouyna, I., Tekaia, F., Beauvais, A., Debeaupuis, J.P., and Nierman, W. (2005) Specific molecular features in the organization and biosynthesis of the cell wall of *Aspergillus fumigatus*. *Med Mycol* **43 Suppl 1**: S15–S22.
- Lee, B.N., and Adams, T.H. (1994) The *Aspergillus nidulans fluG* gene is required for production of an extracellular developmental signal and is related to prokaryotic glutamine synthetase I. *Genes Dev* **8**: 641–51.
- Lee, J., and Paetzel, M. (2011) Structure of the catalytic domain of glucoamylase from *Aspergillus niger*. *Acta Crystallogr* **F67**: 188–192.
- Lee, J.I., Choi, J.H., Park, B.C., Park, Y.H., Lee, M.Y., Park, H.M., and Maeng, P.J. (2004) Differential expression of the chitin synthase genes of *Aspergillus nidulans*, *chsA*, *chsB*, and *chsC*, in response to developmental status and environmental factors. *Fungal Genet Biol* **41**: 635–646.
- Lee, M.-K., Kwon, N.-J., Choi, J.M., Lee, I.-S., Jung, S., and Yu, J.-H. (2014) NsdD is a key repressor of asexual development in *Aspergillus nidulans*. *Genetics* **197**: 159–73.
- Levin, A.M., Vries, R.P. de, Conesa, A., Bekker, C. de, Talon, M., Menke, H.H., *et al.* (2007) Spatial differentiation in the vegetative mycelium of *Aspergillus niger*. *Eukaryot Cell* **6**: 2311–22.
- Li, A., Pfelzer, N., Zuijderwijk, R., and Punt, P. (2012) Enhanced itaconic acid production in *Aspergillus niger* using genetic modification and medium optimization. *BMC Biotechnol* **12**: 57–65.
- Liu, Y., and Levine, B. (2015) Autosis and autophagic cell death: The dark side of autophagy. *Cell Death Differ* **22**: 367–376.
- Lü, Y., Yang, H., Hu, H., Wang, Y., Rao, Z., and Jin, C. (2009) Mutation of Trp137 to glutamate completely removes transglycosyl activity associated with the *Aspergillus fumigatus* AfChiB1. *Glycoconj J* **26**: 525–534.
- MacKenzie, D.A., Guillemette, T., Al-Sheikh, H., Watson, A.J., Jeenes, D.J., Wongwathanarat, P., *et al.* (2005) UPR-independent dithiothreitol stress-induced genes in *Aspergillus niger*. *Mol Genet Genomics* **274**: 410–418.

- Malavazi, I., Lima, J.F., Castro, P.A. de, Savoldi, M., Souza Goldman, M.H. de, and Goldman, G.H. (2008) Genetic interactions of the *Aspergillus nidulans* atmA ATM homolog with different components of the DNA damage response pathway. *Genetics* **178**: 675–91.
- Malavazi, I., Savoldi, M., Silva Ferreira, M.E. da, Soriani, F.M., Bonato, P.S., Souza Goldman, M.H. de, and Goldman, G.H. (2007) Transcriptome analysis of the *Aspergillus nidulans* AtmA (ATM, Ataxia-Telangiectasia mutated) null mutant. *Mol Microbiol* **66**: 74–99.
- Malavazi, I., Semighini, C.P., Kress, M.R. von Z., Harris, S.D., and Goldman, G.H. (2006) Regulation of hyphal morphogenesis and the DNA damage response by the *Aspergillus nidulans* ATM homolog AtmA. *Genetics* **173**: 99–109.
- Manjithaya, R., Anjard, C., Loomis, W.F., and Subramani, S. (2010) Unconventional secretion of *Pichia pastoris* Acb1 is dependent on GRASP protein, peroxisomal functions, and autophagosome formation. *J Cell Biol* **188**: 537–546.
- Martens-Uzunova, E.S., and Schaap, P.J. (2009) Assessment of the pectin degrading enzyme network of *Aspergillus niger* by functional genomics. *Fungal Genet Biol* **46 Suppl 1**: S170–S179.
- Mathew, R., Kongara, S., Beaudoin, B., Karp, C.M., Bray, K., Degenhardt, K., et al. (2007) Autophagy suppresses tumor progression by limiting chromosomal instability. *Genes Dev* 1367–1381.
- Matsui, A., Kamada, Y., and Matsuura, A. (2013) The Role of Autophagy in Genome Stability through Suppression of Abnormal Mitosis under Starvation. *PLoS Genet* **9**.
- Matsuura, A., Tsukada, M., Wada, Y., and Ohsumi, Y. (1997) Apg1p, a novel protein kinase required for the autophagic process in *Saccharomyces cerevisiae*. *Gene* **192**: 245–250.
- Mattern, I.E., Noort, J.M. van, Berg, P. van den, Archer, D.B., Roberts, I.N., and Hondel, C.A. van den (1992) Isolation and characterization of mutants of *Aspergillus niger* deficient in extracellular proteases. *Mol Gen Genet* **234**: 332–6.
- Mattern, I.E., Punt, P.J., and Hondel, C.A.M.J.J. Van den (1988) A vector for *Aspergillus* transformation conferring phleomycin resistance. *Fungal Genet Rep* **35**: 25.
- Maubon, D., Park, S., Tanguy, M., Huerre, M., Schmitt, C., Prévost, M.C., et al. (2006) AGS3, an $\alpha(1-3)$ glucan synthase gene family member of *Aspergillus fumigatus*, modulates mycelium growth in the lung of experimentally infected mice. *Fungal Genet Biol* **43**: 366–375.
- McIntyre, M., Berry, D.R., and McNeil, B. (2000) Role of proteases in autolysis of *Penicillium chrysogenum* chemostat cultures in response to nutrient depletion. *Appl Microbiol Biotechnol* **53**: 235–42.
- McNeil, B., Berry, D.R., Harvey, L.M., Grant, A., and White, S. (1998) Measurement of autolysis in submerged batch cultures of *Penicillium chrysogenum*. *Biotechnol Bioeng* **57**: 297–305.
- Meyer, V., Ram, A.F.J., and Punt, P.J. (2010) Genetics, genetic manipulation, and approaches to strain improvement of filamentous fungi. In *Manual of Industrial Microbiology and Biotechnology*. Baltz, R.H., Demain, A.L., and Davies, J.E. (eds). Washington, DC: ASM Press pp. 318–329.
- Mochida, K., Oikawa, Y., Kimura, Y., Kirisako, H., Hirano, H., Ohsumi, Y., and Nakatogawa, H. (2015) Receptor-mediated selective autophagy degrades the endoplasmic reticulum and the nucleus. *Nature* **522**: 359–362.

- Molnár, Z., Emri, T., Zavaczki, E., Pusztahelyi, T., and Pócsi, I. (2006) Effects of mutations in the GanB/RgsA G protein mediated signalling on the autolysis of *Aspergillus nidulans*. *J Basic Microbiol* **46**: 495–503.
- Molnár, Z., Mészáros, E., Szilágyi, Z., Rosén, S., Emri, T., and Pócsi, I. (2004) Influence of fadAG203R and deltaflbA mutations on morphology and physiology of submerged *Aspergillus nidulans* cultures. *Appl Biochem Biotechnol* **118**: 349–60.
- Mouyna, I., Sarfati, J., Recco, P., Fontaine, T., Henrissatz, B., and Latge, J.P. (2002) Molecular characterization of a cell wall-associated beta(1-3)endoglucanase of *Aspergillus fumigatus*. *Med Mycol* **40**: 455–464.
- Müller, M., Schmidt, O., Angelova, M., Faserl, K., Weys, S., Kremser, L., et al. (2015) The coordinated action of the MVB pathway and autophagy ensures cell survival during starvation. *Elife* **2015**: 1–25.
- Munster, J.M. van, Daly, P., Delmas, S., Pullan, S.T., Blythe, M.J., Malla, S., et al. (2014) The role of carbon starvation in the induction of enzymes that degrade plant-derived carbohydrates in *Aspergillus niger*. *Fungal Genet Biol* **72**: 34–47.
- Munster, J.M. van, Dobruchowska, J.M., Veloo, R., Dijkhuizen, L., and Maarel, M.J.E.C. van der (2015a) Characterization of the starvation-induced chitinase CfcA and α -1,3-glucanase AgnB of *Aspergillus niger*. *Appl Microbiol Biotechnol* **99**: 2209–23.
- Munster, J.M. van, Kaaij, R.M. van der, Dijkhuizen, L., and Maarel, M.J.E.C. van der (2012) Biochemical characterization of *Aspergillus niger* CfcI, a glycoside hydrolase family 18 chitinase that releases monomers during substrate hydrolysis. *Microbiology* **158**: 2168–2179.
- Munster, J.M. van, Nitsche, B.M., Akeroyd, M., Dijkhuizen, L., Maarel, M.J.E.C. van der, and Ram, A.F.J. (2015b) Systems approaches to predict the functions of glycoside hydrolases during the life cycle of *Aspergillus niger* using developmental mutants $\Delta brlA$ and $\Delta flbA$. *PLoS One* **10**: e0116269.
- Munster, J.M. van, Nitsche, B.M., Krijghsheld, P., Wijk, A. van, Dijkhuizen, L., Wösten, H.A., et al. (2013) Chitinases CtcB and CfcI modify the cell wall in sporulating aerial mycelium of *Aspergillus niger*. *Microbiology* **159**: 1853–1867.
- Munster, J.M. van, Sanders, P., Kate, G.A. ten, Dijkhuizen, L., and Maarel, M.J.E.C. van der (2015c) Kinetic characterization of *Aspergillus niger* chitinase CfcI using a HPAEC-PAD method for native chitin oligosaccharides. *Carbohydr Res* **407**: 73–8.
- Nevalainen, H., and Peterson, R. (2014) Making recombinant proteins in filamentous fungi- Are we expecting too much? *Front Microbiol* **5**: 1–10.
- Nikoletopoulou, V., Markaki, M., Palikaras, K., and Tavernarakis, N. (2013) Crosstalk between apoptosis, necrosis and autophagy. *Biochim Biophys Acta-Mol Cell Res* **1833**: 3448–3459.
- Nitsche, B.M., Burggraaf-Van Welzen, A.-M., Lamers, G., Meyer, V., and Ram, A.F.J. (2013) Autophagy promotes survival in aging submerged cultures of the filamentous fungus *Aspergillus niger*. *Appl Microbiol Biotechnol* **97**: 8205–8218.
- Nitsche, B.M., Crabtree, J., Cerqueira, G.C., Meyer, V., Ram, A.F.J., and Wortman, J.R. (2011) New resources for functional analysis of omics data for the genus *Aspergillus*. *BMC Genomics* **12**: 486.

- Nitsche, B.M., Jørgensen, T.R., Akeroyd, M., Meyer, V., and Ram, A.F. (2012) The carbon starvation response of *Aspergillus niger* during submerged cultivation: Insights from the transcriptome and secretome. *BMC Genomics* **13**: 380–402.
- Nuero, O.M., Alfonso, C., Amo, F. Del, and Reyes, F. (1993) Study of β -1,3-glucanase activity during autolysis of *Aspergillus nidulans* by FPLC ion-exchange chromatography. *Lett Appl Microbiol* **17**: 104–108.
- Onodera, J., and Ohsumi, Y. (2005) Autophagy is required for maintenance of amino acid levels and protein synthesis under nitrogen starvation. *J Biol Chem* **280**: 31582–31586.
- Otto, C., Hoffmann, S., Gorodkin, J., and Stadler, P.F. (2011) Fast local fragment chaining using sum-of-pair gap costs. *Algorithms Mol Biol* **6**: 4.
- Paeye, N., Jung, S., Schäpe, P., Müller-Hagen, D., Ouedraogo, J.-P., Heiderich, C., et al. (2016) A Transcriptome Meta-Analysis Proposes Novel Biological Roles for the Antifungal Protein AnAFP in *Aspergillus niger*. *PLoS One* **11**: e0165755.
- Papáčková, Z., and Cahová, M. (2014) Important role of autophagy in regulation of metabolic processes in health, disease and aging. *Physiol Res* **63**: 409–20.
- Park, C., and Zhang, J. (2011) Genome-wide evolutionary conservation of N-glycosylation sites. *Mol Biol Evol* **28**: 2351–7.
- Park, H.-S., and Yu, J.-H. (2012) Genetic control of asexual sporulation in filamentous fungi. *Curr Opin Microbiol* **15**: 669–77.
- Park, Y.E., Hayashi, Y.K., Bonne, G., Arimura, T., Noguchi, S., Nonaka, I., and Nishino, I. (2009) Autophagic degradation of nuclear components in mammalian cells. *Autophagy* **5**: 795–804.
- Peberdy, J.F. (1994) Protein secretion in filamentous fungi—trying to understand a highly productive black box. *Trends Biotechnol* **12**: 50–57.
- Pel, H.J., Winde, J.H. de, Archer, D.B., Dyer, P.S., Hofmann, G., Schaap, P.J., et al. (2007) Genome sequencing and analysis of the versatile cell factory *Aspergillus niger* CBS 513.88. *Nat Biotechnol* **25**: 221–31.
- Perez-Leblic, M.I., Reyes, F., Martinez, M.J., and Lahoz, R. (1982) Cell wall degradation in the autolysis of filamentous fungi. *Mycopathologia* **80**: 147–55.
- Petersen, T.N., Brunak, S., Heijne, G. von, and Nielsen, H. (2011) SignalP 4.0: discriminating signal peptides from transmembrane regions. *Nat Methods* **8**: 785–6.
- Pinan-Lucarré, B., Balguerie, A., and Clavé, C. (2005) Accelerated cell death in *Podospora* autophagy mutants. *Eukaryot Cell* **4**: 1765–1774.
- Pinar, M., Pantazopoulou, A., and Peñalva, M.A. (2013) Live-cell imaging of *Aspergillus nidulans* autophagy: RAB1 dependence, Golgi independence and ER involvement. *Autophagy* **9**: 1024–1043.
- Pócsi, I., Leiter, E., Kwon, N.-J., Shin, K.-S., Kwon, G.-S., Pusztahelyi, T., et al. (2009) Asexual sporulation signalling regulates autolysis of *Aspergillus nidulans* via modulating the chitinase ChiB production. *J Appl Microbiol* **107**: 514–523.

- Pócsi, I., Miskei, M., Karányi, Z., Emri, T., Ayoubi, P., Pusztahelyi, T., *et al.* (2005) Comparison of gene expression signatures of diamide, H₂O₂ and menadione exposed *Aspergillus nidulans* cultures—Linking genome-wide transcriptional changes to cellular physiology. *BMC Genomics* **6**: 1–18.
- Pollack, J.K., Li, Z.J., and Marten, M.R. (2008) Fungal mycelia show lag time before re-growth on endogenous carbon. *Biotechnol Bioeng* **100**: 458–65.
- Ponpuak, M., Mandell, M. a, Kimura, T., Chauhan, S., Cleyrat, C., and Deretic, V. (2015) Secretory autophagy. *Curr Opin Cell Biol* **35**: 106–116.
- Pu, Y., and Bassham, D.C. (2013) Links between ER stress and autophagy in plants. *Plant Signal Behav* **8**: e24297.
- Pullan, S.T., Daly, P., Delmas, S., Ibbett, R., Kokolski, M., Neiteler, A., *et al.* (2014) RNA-sequencing reveals the complexities of the transcriptional response to lignocellulosic biofuel substrates in *Aspergillus niger*. *Fungal Biol Biotechnol* **1**: 3.
- Punt, P.J., Oliver, R.P., Dingemans, M.A., Pouwels, P.H., and Hondel, C.A. van den (1987) Transformation of *Aspergillus* based on the hygromycin B resistance marker from *Escherichia coli*. *Gene* **56**: 117–124.
- Punt, P.J., Schuren, F.H.J., Lehmebeck, J., Christensen, T., Hjort, C., and Hondel, C.A.M.J.J. van den (2008) Characterization of the *Aspergillus niger* prtT, a unique regulator of extracellular protease encoding genes. *Fungal Genet Biol* **45**: 1591–1599.
- Pusztahelyi, T., Molnár, Z., Emri, T., Klement, E., Miskei, M., Kerékgyártó, J., *et al.* (2006) Comparative studies of differential expression of chitinolytic enzymes encoded by *chiA*, *chiB*, *chiC* and *nagA* genes in *Aspergillus nidulans*. *Folia Microbiol (Praha)* **51**: 547–54.
- Pusztahelyi, T., and Pócsi, I. (2013) Functions, Cooperation, and Interplays of the Vegetative Growth Signaling Pathway in the *Aspergilli*. *J Mycol* **2013**: 1–11.
- Richie, D.L., Fuller, K.K., Fortwendel, J., Miley, M.D., McCarthy, J.W., Feldmesser, M., *et al.* (2007) Unexpected link between metal ion deficiency and autophagy in *Aspergillus fumigatus*. *Eukaryot Cell* **6**: 2437–2447.
- Robert, T., Vanoli, F., Chiolo, I., Shubassi, G., Bernstein, K.A., Rothstein, R., *et al.* (2011) HDACs link the DNA damage response, processing of double-strand breaks and autophagy. *Nature* **471**: 74–9.
- Rodríguez-Urra, A.B., Jiménez, C., Nieto, M.I., Rodríguez, J., Hayashi, H., and Ugalde, U. (2012) Signaling the induction of sporulation involves the interaction of two secondary metabolites in *Aspergillus nidulans*. *ACS Chem Biol* **7**: 599–606.
- Ron, D., and Walter, P. (2007) Signal integration in the endoplasmic reticulum unfolded protein response. *Nat Rev Mol Cell Biol* **8**: 519–529.
- Ruggiano, A., Foresti, O., and Carvalho, P. (2014) ER-associated degradation: Protein quality control and beyond. *J Cell Biol* **204**: 869–879.
- Ruijter, G.J., and Visser, J. (1997) Carbon repression in *Aspergilli*. *FEMS Microbiol Lett* **151**: 103–14.
- Sambrook, J., and Russell, D.W. (2001) *Molecular Cloning: A Laboratory Manual*. New York: Cold Spring Harbor Laboratory Press.

- Sarkar, A., Funk, A.N., Scherlach, K., Horn, F., Schroeckh, V., Chankhamjon, P., *et al.* (2012) Differential expression of silent polyketide biosynthesis gene clusters in chemostat cultures of *Aspergillus nidulans*. *J Biotechnol* **160**: 64–71.
- Sarkar, P., Bosneaga, E., and Auer, M. (2009) Plant cell walls throughout evolution: towards a molecular understanding of their design principles. *J Exp Bot* **60**: 3615–35.
- Scheller, H.V., and Ulvskov, P. (2010) Hemicelluloses. *Annu Rev Plant Biol* **61**: 263–89.
- Schmidt, F.R. (2004) Recombinant expression systems in the pharmaceutical industry. *Appl Microbiol Biotechnol* **65**: 363–372.
- Schrickx, J.M., Krave, A.S., Verdoes, J.C., Hondel, C.A. van den, Stouthamer, A.H., and Verseveld, H.W. van (1993) Growth and product formation in chemostat and recycling cultures by *Aspergillus niger* N402 and a glucoamylase overproducing transformant, provided with multiple copies of the *glaA* gene. *J Gen Microbiol* **139**: 2801–10.
- Sekine, H., Nasuno, S., and Iguchi, N. (1969) Isolation of Highly Proteolytic Mutants from *Aspergillus sojae*. *Agric Biol Chem* **33**: 1477–1482.
- Senft, D., and Ronai, Z. a. (2015) UPR, autophagy, and mitochondria crosstalk underlies the ER stress response. *Trends Biochem Sci* **4**: 1–8.
- Shimizu, K., and Keller, N.P. (2001) Genetic involvement of a cAMP-dependent protein kinase in a G protein signaling pathway regulating morphological and chemical transitions in *Aspergillus nidulans*. *Genetics* **157**: 591–600.
- Shin, K.-S., Kwon, N.-J., Kim, Y.H., Park, H.-S., Kwon, G.-S., and Yu, J.-H. (2009) Differential roles of the ChiB chitinase in autolysis and cell death of *Aspergillus nidulans*. *Eukaryot Cell* **8**: 738–46.
- Shoji, J.Y., Arioka, M., and Kitamoto, K. (2006) Possible involvement of pleiomorphic vacuolar networks in nutrient recycling in filamentous fungi. *Autophagy* **2**: 226–227.
- Shoji, J.Y., and Craven, K.D. (2011) Autophagy in basal hyphal compartments: A green strategy of great recyclers. *Fungal Biol Rev* **25**: 79–83.
- Shoji, J.Y., Kikuma, T., Arioka, M., and Kitamoto, K. (2010) Macroautophagy-mediated degradation of whole nuclei in the filamentous fungus *Aspergillus oryzae*. *PLoS One* **5**.
- Skromne, I., Sánchez, O., and Aguirre, J. (1995) Starvation stress modulates the expression of the *Aspergillus nidulans* *brlA* regulatory gene. *Microbiology* **141**: 21–8.
- Sousa Lima, P. de, Casaletti, L., Bailão, A.M., Vasconcelos, A.T.R. de, Fernandes, G. da R., and Soares, C.M. de A. (2014) Transcriptional and proteomic responses to carbon starvation in *Paracoccidioides*. *PLoS Negl Trop Dis* **8**: e2855.
- Spitzmüller, Z., Kwon, N.-J., Szilágyi, M., Keserű, J., Tóth, V., Yu, J.-H., *et al.* (2015) γ -Glutamyl transpeptidase (GgtA) of *Aspergillus nidulans* is not necessary for bulk degradation of glutathione. *Arch Microbiol* **197**: 285–97.
- Stephan, J.S., Yeh, Y.-Y., Ramachandran, V., Deminoff, S.J., and Herman, P.K. (2009) The Tor and PKA signaling pathways independently target the Atg1/Atg13 protein kinase complex to control autophagy. *Proc Natl Acad Sci U S A* **106**: 17049–17054.

- Stock, J., Sarkari, P., Kreibich, S., Brefort, T., Feldbrügge, M., and Schipper, K. (2012) Applying unconventional secretion of the endochitinase Cts1 to export heterologous proteins in *Ustilago maydis*. *J Biotechnol* **161**: 80–91.
- Suelmann, R., and Fischer, R. (2000) Mitochondrial movement and morphology depend on an intact actin cytoskeleton in *Aspergillus nidulans*. *Cell Motil Cytoskeleton* **45**: 42–50.
- Suzuki, S.W., Onodera, J., and Ohsumi, Y. (2011) Starvation induced cell death in autophagy-defective yeast mutants is caused by mitochondria dysfunction. *PLoS One* **6**: 0–7.
- Szilágyi, M., Anton, F., Forgács, K., Yu, J.-H., Pócsi, I., and Emri, T. (2012) Antifungal activity of extracellular hydrolases produced by autolysing *Aspergillus nidulans* cultures. *J Microbiol* **50**: 849–54.
- Szilágyi, M., Kwon, N.-J., Bakti, F., M-Hamvas, M., Jámbrik, K., Park, H., et al. (2011) Extracellular proteinase formation in carbon starving *Aspergillus nidulans* cultures—physiological function and regulation. *J Basic Microbiol* **51**: 625–34.
- Szilágyi, M., Kwon, N.-J., Dorogi, C., Pócsi, I., Yu, J.-H., and Emri, T. (2010a) The extracellular β -1,3-endoglucanase EngA is involved in autolysis of *Aspergillus nidulans*. *J Appl Microbiol* **109**: 1498–508.
- Szilágyi, M., Miskei, M., Karányi, Z., Lenkey, B., Pócsi, I., and Emri, T. (2013) Transcriptome changes initiated by carbon starvation in *Aspergillus nidulans*. *Microbiology* **159**: 176–190.
- Szilágyi, M., Pócsi, I., Forgács, K., and Emri, T. (2010b) MeaB-dependent nutrition sensing regulates autolysis in carbon starved *Aspergillus nidulans* cultures. *Indian J Microbiol* **50**: 104–8.
- Takashima, S., Iikura, H., Nakamura, A., Masaki, H., and Uozumi, T. (1996) Analysis of Cre1 binding sites in the *Trichoderma reesei cbh1* upstream region. *FEMS Microbiol Lett* **145**: 361–6.
- Thorpe, G.W., Fong, C.S., Alic, N., Higgins, V.J., and Dawes, I.W. (2004) Cells have distinct mechanisms to maintain protection against different reactive oxygen species: Oxidative-stress-response genes. *Proc Natl Acad Sci U S A* **101**: 6564–6569.
- Travers, K.J., Patil, C.K., Wodicka, L., Lockhart, D.J., Weissman, J.S., and Walter, P. (2000) Functional and genomic analyses reveal an essential coordination between the unfolded protein response and ER-associated degradation. *Cell* **101**: 249–258.
- Tsukada, M., and Ohsumi, Y. (1993) Isolation and characterization of autophagy-defective mutants of *Saccharomyces cerevisiae*. *FEBS Lett* **333**: 169–174.
- Tucker, C.L., and Fields, S. (2004) Quantitative genome-wide analysis of yeast deletion strain sensitivities to oxidative and chemical stress. *Comp Funct Genomics* **5**: 216–224.
- Twumasi-Boateng, K., Yu, Y., Chen, D., Gravelat, F.N., Nierman, W.C., and Sheppard, D.C. (2009) Transcriptional profiling identifies a role for BrlA in the response to nitrogen depletion and for StuA in the regulation of secondary metabolite clusters in *Aspergillus fumigatus*. *Eukaryot Cell* **8**: 104–115.
- Vallim, M.A., Miller, K.Y., and Miller, B.L. (2000) *Aspergillus* SteA (sterile12-like) is a homeodomain-C2/H2-Zn+2 finger transcription factor required for sexual reproduction. *Mol Microbiol* **36**: 290–301.
- Vembar, S.S., and Brodsky, J.L. (2008) One step at a time: endoplasmic reticulum-associated degradation. *Nat Rev Mol Cell Biol* **9**: 944–957.

- Veneault-Fourrey, C., Barooah, M., Egan, M., Wakley, G., and Talbot, N.J. (2006) Autophagic fungal cell death is necessary for infection by the rice blast fungus. *Science* **312**: 580–3.
- Vilchez, D., Saez, I., and Dillin, A. (2014) Organismal Ageing and Age-Related Diseases. *Nat Commun* **5**: 1–13.
- Vinck, A., Terlouw, M., Pestman, W.R., Martens, E.P., Ram, A.F., Hondel, C.A.M.J.J. Van Den, and Wösten, H.A.B. (2005) Hyphal differentiation in the exploring mycelium of *Aspergillus niger*. *Mol Microbiol* **58**: 693–699.
- Vishniac, W., and Santer, M. (1957) The *Thiobacilli*. *Bacteriol Rev* **21**: 195–213.
- Vogel, J. (2008) Unique aspects of the grass cell wall. *Curr Opin Plant Biol* **11**: 301–7.
- Vries, R.P. de, Visser, J., and Graaff, L.H. de (1999) CreA modulates the XlnR-induced expression on xylose of *Aspergillus niger* genes involved in xylan degradation. *Res Microbiol* **150**: 281–5.
- Wang, F., Krijgsheld, P., Hulsman, M., Bekker, C. de, Müller, W.H., Reinders, M., et al. (2015) FluG affects secretion in colonies of *Aspergillus niger*. *Antonie van Leeuwenhoek, Int J Gen Mol Microbiol* **107**: 225–240.
- Wang, Y., Xue, W., Sims, A.H., Zhao, C., Wang, A., Tang, G., et al. (2008) Isolation of four pepsin-like protease genes from *Aspergillus niger* and analysis of the effect of disruptions on heterologous laccase expression. *Fungal Genet Biol* **45**: 17–27.
- Wei, H., Scherer, M., Singh, A., Liese, R., and Fischer, R. (2001) *Aspergillus nidulans* alpha-1,3 glucanase (mutanase), *mutA*, is expressed during sexual development and mobilizes mutan. *Fungal Genet Biol* **34**: 217–227.
- White, S., McIntyre, M., Berry, D.R., and McNeil, B. (2002) The autolysis of industrial filamentous fungi. *Crit Rev Biotechnol* **22**: 1–14.
- Xia, G., Jin, C., Zhou, J., Yang, S., Zhang, S., and Jin, C. (2001) A novel chitinase having a unique mode of action from *Aspergillus fumigatus* YJ-407. *Eur J Biochem* **268**: 4079–4085.
- Xie, Z., and Klionsky, D.J. (2007) Autophagosome formation: core machinery and adaptations. *Nat Cell Biol* **9**: 1102–1109.
- Xiong, Y., Coradetti, S.T., Li, X., Gritsenko, M.A., Clauss, T., Petyuk, V., et al. (2014) The proteome and phosphoproteome of *Neurospora crassa* in response to cellulose, sucrose and carbon starvation. *Fungal Genet Biol* **72**: 21–33.
- Yamazaki, H., Tanaka, A., Kaneko, J., Ohta, A., and Horiuchi, H. (2008) *Aspergillus nidulans* ChiA is a glycosylphosphatidylinositol (GPI)-anchored chitinase specifically localized at polarized growth sites. *Fungal Genet Biol* **45**: 963–72.
- Yamazaki, H., Yamazaki, D., Takaya, N., Takagi, M., Ohta, A., and Horiuchi, H. (2007) A chitinase gene, *chiB*, involved in the autolytic process of *Aspergillus nidulans*. *Curr Genet* **51**: 89–98.
- Yang, Z., Huang, J., Geng, J., Nair, U., and Klionsky, D.J. (2006) Atg22 recycles amino acids to link the degradative and recycling functions of autophagy. *Mol Biol Cell* **17**: 5094–5104.
- Ye, X.S., Lee, S.L., Wolkow, T.D., McGuire, S.L., Hamer, J.E., Wood, G.C., and Osmani, S.A. (1999) Interaction between developmental and cell cycle regulators is required for morphogenesis in *Aspergillus nidulans*. *EMBO J* **18**: 6994–7001.

- Yoon, J., Kikuma, T., Maruyama, J., and Kitamoto, K. (2013) Enhanced production of bovine chymosin by autophagy deficiency in the filamentous fungus *Aspergillus oryzae*. *PLoS One* **8**: e62512.
- Yoon, J., Kimura, S., Maruyama, J., and Kitamoto, K. (2009) Construction of quintuple protease gene disruptant for heterologous protein production in *Aspergillus oryzae*. *Appl Microbiol Biotechnol* **82**: 691–701.
- Yoon, J., Maruyama, J., and Kitamoto, K. (2011) Disruption of ten protease genes in the filamentous fungus *Aspergillus oryzae* highly improves production of heterologous proteins. *Appl Microbiol Biotechnol* **89**: 747–759.
- Yu, J.-H. (2006) Heterotrimeric G protein signaling and RGSs in *Aspergillus nidulans*. *J Microbiol* **44**: 145–54.
- Zhang, M., and Schekman, R. (2013) Cell biology. Unconventional secretion, unconventional solutions. *Science* **340**: 559–61.
- Zhang, Y., Qi, H., Taylor, R., Xu, W., Liu, L.F., and Jin, S. (2007) The role of autophagy in mitochondria maintenance: Characterization of mitochondrial functions in autophagy-deficient *S. cerevisiae* strains. *Autophagy* **3**: 337–346.
- Zhao, W., Li, C., Liang, J., and Sun, S. (2014) The *Aspergillus fumigatus* β -1,3-glucanosyltransferase Gel7 plays a compensatory role in maintaining cell wall integrity under stress conditions. *Glycobiology* **24**: 418–427.
- Zonneveld, B.J. (1972) Morphogenesis in *Aspergillus nidulans*. The significance of a alpha-1, 3-glucan of the cell wall and alpha-1, 3-glucanase for cleistothecium development. *Biochim Biophys Acta* **273**: 174–87.
- Zonneveld, B.J. (1974) Alpha-1,3 glucan synthesis correlated with alpha-1,3 glucanase synthesis, conidiation and fructification in morphogenetic mutants of *Aspergillus nidulans*. *J Gen Microbiol* **81**: 445–51.
- Zustiak, M.P., Pollack, J.K., Marten, M.R., and Betenbaugh, M.J. (2008) Feast or famine: autophagy control and engineering in eukaryotic cell culture. *Curr Opin Biotechnol* **19**: 518—526.

Supplementary material

Chapter 2

Figure S1 Southern analysis for the transformation of the *PgpdA-NcitA::gfp-TtrpC-pyrG** construct into *A. niger* strain AB4.1

Figure S2 Southern analyses for *atg1*, *atg8* and *atg17* deletions in the N402 background

Figure S3 Southern analyses for *atg1*, *atg8* and *atg17* deletions in the BN38.9 background

Figure S4 Southern analyses for complementation of $\Delta atg1$, $\Delta atg8$ and $\Delta atg17$ in BN56.2, BN57.1 and BN58.1 backgrounds

Figure S5 Complementation studies for sensitivity phenotypes

Table S1 Primers used in this study

Chapter 3

Table S1 Genome-wide transcriptome data of *A. niger* $\Delta atg1$ compared to *A. niger* N402

Table S2 Enriched GO-terms related to bioprocesses among differentially expressed genes

Chapter 4

Figure S1 Southern analyses for *atg* deletions in MA78.6, MA97.2, MA134.64 and MA136.18 backgrounds

Figure S2 Amino acid sequence of the *A. niger* glucoamylase protein

Figure S3 Southern analyses for the integration of *PgpdA-wtglaA::gfp-TtrpC-pyrG*** and *PgpdA-mtglaA::gfp-TtrpC-pyrG*** constructs on the *pyrG* locus in MA169.4, AW27.10, AW28.12 and AW30.3 backgrounds

Chapter 5

Figure S1 Southern analysis for the deletion of *pepN* in MA234

Figure S2 Amino acid sequence of the *A. niger* PepN protein

Figure S3 Alignment of the amino acid sequences of PepA and PepN orthologs using Clustal Omega

List of publications

Jørgensen, T.R., **Burggraaf, A.-M.**, Arentshorst, M., Schutze, T., Lamers, G., Niu, J., Kwon, M.J., Park, J., Frisvad, J.C., Nielsen, K.F. Meyer, V., Hondel, C.A.M.J.J. van den, Dyer, P.S., and Ram, A.F.J. (2020) Identification of SclB, a Zn(II)2Cys6 transcription factor involved in sclerotium formation in *Aspergillus niger*. *Fungal Genet Biol* **139**: 103377.

Burggraaf, A.-M., Punt, P.J., and Ram, A.F.J. (2016) The unconventional secretion of PepN is independent of a functional autophagy machinery in the filamentous fungus *Aspergillus niger*. *FEMS Microbiol Lett* **363**: fnw152.

Burggraaf, A.-M., and Ram, A.F.J. (2016) Autophagy is dispensable to overcome ER stress in the filamentous fungus *Aspergillus niger*. *Microbiologyopen* **5**: 647–658.

Munster, J.M. van, **Burggraaf, A.-M.**, Pócsi, I., Szilágyi, M., Emri, T., and Ram, A.F.J. (2016) Post-genomic Approaches to Dissect Carbon Starvation Responses in *Aspergilli*. In *Aspergillus and Penicillium in the post-genomic era*. Caister Academic Press pp. 89–112.

Nitsche, B.M., **Burggraaf-van Welzen, A.-M.**, Lamers, G., Meyer, V., and Ram, A.F.J. (2013) Autophagy promotes survival in aging submerged cultures of the filamentous fungus *Aspergillus niger*. *Appl Microbiol Biotechnol* **97**: 8205–8218.

Jørgensen, T.R., Park, J., Arentshorst, M., **Welzen, A.-M. van**, Lamers, G., VanKuyk, P.A., Damveld, R.A., Hondel, C.A.M.J.J. van den, Nielsen, K.F., Frisvad, J.C., and Ram, A.F.J. (2011) The molecular and genetic basis of conidial pigmentation in *Aspergillus niger*. *Fungal Genet Biol* **48**: 544–553.

Curriculum vitae

Anne-Marie Burggraaf werd geboren op 24 februari 1988 te Alphen aan den Rijn en groeide op in Stolwijk. Na het behalen van haar VWO diploma in 2006, studeerde ze Biologie aan de Universiteit Leiden. Tijdens haar master Molecular and Cellular Biosciences deed zij een onderzoeksproject bij de afdeling Molecular Microbiology and Biotechnology. In 2011 studeerde ze cum laude af en begon in dezelfde onderzoeksgroep aan het promotieonderzoek wat resulteerde in dit proefschrift. Anne-Marie werkt momenteel als data engineer bij Eneco.

