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JUNTA DE
CASTILLA Y
LEON

INSTITUTO DE MICROBIOLOGÍA BIOQUÍMICA

(Institute of Biochemical Microbiology)

Joint Centre:

VNiVERSiTY OF SALAMANCA (VSAL)
&
SPANISH NATIONAL RESEARCH COUNCIL
(CONSEJO SUPERIOR DE INVESTIGACIONES CIENTÍFICAS)
(CSIC)

Line "CELL WALL AND MORPHOGENESIS IN YEAST" Research activity (2003-2008)

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1a. CURRENT MEMBERS

Staff

Dr. Angel Durán (CSIC Research Scientist). **Dr. Juan C. Ribas** (CSIC Associate Scientist).
(1-3)ß-D-glucan biosynthesis in *Shizosaccharomyces pombe*. Role of the **Bgsp** catalytic subunits.

Dr. César Roncero (USAL Associate Professor). Regulation of chitin biosynthesis in the fungal cell wall.

Dr. Francisco del Rey (USAL Full Professor). **Dr. Carlos R. Vázquez de Aldana** (CSIC Research Scientist). Morphogenesis and cell separation in yeasts.

Dr. Mª Henar Valdivieso (USAL Associate Professor). Role of proteins involved in yeast cell wall synthesis in cytokinesis, polarity and sexual differentiation.

Dr. Pilar Pérez (CSIC Research Professor). **Dr. Beatriz Santos** (USAL permanent contracted Associate Professor). **Dr. Pedro M. Coll** (USAL contracted Associate Professor). Signalling pathways of the Rho GTPases.

Dr. Yolanda Sánchez (USAL Associate Professor). Role of Rho1p GEFs in polarity control, cytokinesis and cell integrity in fission yeast.

Postdoctorals

Dr. Alberto González-Novo (supervisor: C. R. Vazquez. de Aldana)
Dra. Jacqueline Pérez (supervisor: C. Roncero)
Dr. Sergio Rincón (supervisor: P. Pérez and B. Santos)
Dra. Maria de Medina (supervisor: C. R. Vázquez de Aldana)

Ph. D. ongoing projects

- Abigail Reyes (supervisor: C. Roncero) (2004-2008). Molecular mechanisms involved in the activation of chitin synthase III in filamentous fungi.
- Patricia García (supervisor: Y. Sánchez) (2004-2008). Characterization of *rgf1*$^{+}$ and *rgf2*$^{+}$, as possible regulators of (1,3)ß-D-glucan biosynthesis in *S. pombe*.
- Mª Antonia Villar (supervisor: P. Pérez). (2005-2008). Regulation of *rho* GTPases family in *S. pombe*.
- Mohammad R. Sharifmoghadam (supervisor: Mª H. Valdivieso) (2005-2008) (Iran Gov. fellowship). Characterization of genes involved in the cellular fusion process of *S. pombe.*
- Javier Muñoz (supervisor: J. C. Ribas). (2006-2009). Regulation of the catalytic subunits of fission yeast β(1,3)-D-glucan synthases and their use for the design and characterization of new antifungal agents.
- Javier Encinar (supervisors: C. R. Vázquez de Aldana and F. del Rey) (2006-2009). Studies on the processes of regulation and assembly of the fungal cell wall.
- Mario Pinar (supervisor: P. Pérez) (2006-2009). Regulation of morphogenesis in *S. pombe* by the family of rho GTPases.
- Alberto Gómez (supervisor: C. Roncero) (2006-2009). Signalling cascades and the control of fungal cell wall assembly.
- José A. Clemente (supervisor: Mª H. Valdivieso and J. C. Ribas). (2007-2010). Mechanism of cell fusion during the process of mating in *S. pombe*
- Mariona Ramos (supervisor: J.C. Ribas and A. Durán) (2007-2010). Bgs1p role in the processes of polarity and cytokinesis in *S. pombe*.
- Carlos Sacristán (supervisor: C. Roncero) (2008-2011). Structure-function relationship among fungal chitin synthases belonging to class 2 family.
- Sandra M. Cruz (supervisor: Y. Sánchez) (2008-2010). Cell wall integrity sensors in the fission yeast *S. pombe*.
- Raul Alonso (supervisor: P. Pérez) (2008-2012).
- Miguel Estravis (supervisor: P. Pérez) (2008-2012).
- Nagore T. de León (supervisor: Mª H. Valdivieso) (2008-2012).
- Diana M. Calderón (supervisors: C. R. Vázquez de Aldana and F. del Rey) (2008-2012).
- Mahdi Shahriari (supervisor: Mª H. Valdivieso) (2008-2012).

Supporting personnel

- Elvira Portales (temporal IMB technician assigned part time to one group)
- Belen Moreno (technician assigned by grant to one group)
- Rosario Valle (technician assigned by grant to one group)
- Yolanda Arnaiz (technician assigned by grant to one group)
- Susana Fernández (temporal IMB technician assigned part time to one group)

1b. FORMER MEMBERS (Ph. D. students, since 2001)

- Ivone M. Pereira (J.C. Ribas and A. Durán)
- Cristina Jiménez (C. Roncero)
- Virginia Tajadura (Y. Sánchez)
- Ignacio García (Y. Sánchez)
- Juan Carlos García (J. C. Ribas and A. Durán)
- María Sanz (C. Roncero)
- Elena Carnero (Y. Sánchez y A. Durán)
- Victoria Martín (Y. Sánchez)
- Teresa Mateo (P. Pérez)
- María Luisa Alonso (F. del Rey and C. R. V. de Aldana)
- Eva P. Hernando (F. del Rey and C. R. V. de Aldana)
- Rebeca García (H. Valdivieso)
- Ana Belén Martín (F. del Rey and C. R. V. de Aldana)
- Luís García (C. Roncero)
- Blanca García (Y. Sánchez)
- Hugo Cartagena (H. Valdivieso y A. Durán)
- Sandra Ufano (F. del Rey and C. R. V. de Aldana)

2. RESEARCH SUMMARY

The cell wall is a vital structure, external to the plasma membrane that confers mechanical and osmotic support to the fungal cell. The aim of the group is to characterize the function and regulation of the proteins required for the construction and remodelling of this structure. The fungal cell wall is not only a morphogenetic model but a validated target to search for new antifungal agents with selective toxicity.

The (1-3)β-D-glucan is one of the most important structural polymers of the fungal cell wall. We are studying the function of the 4 essential proteins of the Bgs family, as the catalytic subunits of the (1-3)β-D-glucan biosynthesis, using the fission yeast *Schizosaccharomyces pombe* as a model. We will focus particularly on the analysis of the regions of these genes/proteins involved in the resistance to new antifungal agents (i.e.: cancidas) and on the design of autolytic strains to produce cell extracts by gentle means and/or to use *S. pombe* as a factory to produce proteins.

(1-3)β-D-glucan biosynthesis does not depend exclusively on the biosynthetic activities but on many other regulatory proteins. For that reason, we are also studying the cascade pathways regulated by the Rho-type GTPases as main actors in the activation and localization of (1,3)β and (1,3)α-D-glucan synthases, the organization of the actin cytoskeleton and the polarity secretion, all of them essential processes required for the cell wall biosynthesis in *S. pombe*. By this mean, fungal cell wall biosynthesis is closely related to processes such as cytokinesis and polar growth. There are six Rho-type GTPase proteins in *S. pombe* (Rho1-Rho5 and Cdc42), ten negative regulator proteins (GAPs) and eight activator proteins that favours the GTP binding (GEFs), all of them affecting cellular morphogenesis and cell wall biosynthesis in *S. pombe*.

Chitin is another essential polymer of the fungal cell wall. We are studying the process of chitin biosynthesis and its regulation using the budding yeast *Saccharomyces cerevisiae* as a model and characterizing the chitin synthase activities from other fungal models (pathogenic fungi such as *Aspergillus fumigatus* and *Cryptococcus*). We want to develop HTS type assays to be applied in the selection of new inhibitors of these chitin synthase activities. In addition, fungal cells respond to cell wall damages by different remedial mechanisms, one of them is overactivation of chitin synthesis. We will explore the role of several signalling pathways (HOG, PKC or RIM) in the maintenance of cell integrity.

The fungal cell wall in spite of its rigidity is a very dynamic structure. The cell wall is always growing and the remodelling is constantly in progress to allow the cell to adapt to the morphogenetic changes that take place during the different stages of the life cycle. Therefore, we are analyzing the mechanisms that coordinate synthesis and degradation of the yeast septum (cytokinesis and cell separation) or cell fusion, with other events of the cell cycle and analyzing the involvement of the mechanisms that participate in the cell cycle progression (cyclin-Cdk complexes) and the exit of mitosis (MEN or SIN pathways) in the regulation of cell separation by using different yeast models such as *S. cerevisiae*, *S. pombe* and *Candida albicans*.

Finally, the availability of a *S. pombe* genomic collection of deletants of every single gene will allow us, by the design of different genomic screenings, to identify new genes needed for cell wall biosynthesis and to unravel the functional relationships among key molecules that control the geometry of cell growth (synthases, Rho GTPases and their regulators, lytic or remodelling enzymes, septins, etc.).

3. PUBLICATIONS (A: original articles; R: reviews; C: book chapters).

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VILLAR-TAJADURA, M. A., COLL, P. M., MADRID, M., CANSADO, J., SANTOS, B., **PEREZ, P**. 2008. Rga2 IS A Rho2 GAP That regulates morphogenesis and cell integrity in *Schizosaccharomyces pombe.* Mol Microbiol. (in press). A. F. I. = 5.462

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ALONSO-NUÑEZ, M. L., AN, H., MARTIN-CUADRADO, A. B., METHA, S., PETIT, C., SIPICZKI, M., **DEL REY, F.**, GOULD, K., **VAZQUEZ DE ALDANA, C.** 2005. Ace2p controls the expression of genes required for cell separation in *Schizosaccharomyces pombe*. Mol. Biol. Cell 16: 2003-2017. A. F. I. = 6.520

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4. PATENTS

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5. RESEARCH GRANTS (**EC**: European Community; **CICYT**: Spanish National Committee for Science and Technology, **JCYL**: Regional Government) (Regular Regional Government grants not included).

Fungal cell wall biogenesis and cell growth: searching targets for new antifungal agents. Dr. A. Durán. **JCYL** (GR231). 2008-2010.

Regulation of morphogenesis, cell growth and fungal cell wall biosynthesis by GTPases. Dra. P. Pérez. **CICYT** (BFU2007-60675). 2007-2010.

Morphogenesis and cell separation in yeast. Dr. C. R. Vázquez de Aldana. **CICYT (**BFU2007-60390/BMC). 2007-2010.

Fungal chitin synthases and their role in cell viability: a new step in the search of new antifungal agents. Dr. C. Roncero. **CICYT** (BIO2007-60779). 2007-2010.

Yeast morphogenesis. Role of regulatory proteins in cytokinesis. Dra. H. Valdivieso. **CICYT** (BFU2007-61866). 2007-2010.

(1,3)β-D-glucan synthase catalytic subunits and the integrity, polarity and cytokinesis of *Schizosaccharomyces pombe*. Biotechnological tools and targets to search for antifungal agents. Dr. J. C. Ribas. **CICYT** (BIO2006-13566). 2007-2009.

Characterization of new regulators of *Schizosaccharomyces pombe* GTPases and its involvement in morphogenesis. Dr. Y. Sánchez. **CICYT** (BFU-2005-01557). 2006-2008.

The fungal cell wall as a target for antifungal therapies (FUNGWALL). Dr. C. R. Vázquez de Aldana (including groups from Drs. F. del Rey and C. Roncero) **EC** (LSHB-CT-2004-511952). 2005-2007.

Regulation of chitin biosynthesis in fungi and its posible used as antifungal target. Dr. C. Roncero (Dr. A. Durán included). **CICYT** (BIO2004-00280). 2005-2007.

Rho family GTPases and regulation of yeast cell wall biosynthesis. Useful targets for the development of new antifungal agents. Dr. P. Pérez. **CICYT** (BIO2004-00384). 2005-2007.

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Functional analysis of fungal cell wall (1,3)ß-D-glucan biosynthesis: a morphogenetic model and a tools in the search for new antifungal agents. Dr. J.C. Ribas. **CICYT** (BIO2003-01040). 2003-2006.

Chitin biosynthesis in yeast: a tool in the search for new antifungal agents. Dr. C. Roncero (Drs. A. Durán and M. H. Valdivieso included). **CICYT** (BIO2001-2048). 2002-2004.

Regulation of fungal cell wall biosynthesis by the RHO family GTPases. Useful targets for the development of new antifungal agents. Dr. P. Pérez. **CICYT** (BIO2001-1531). 2002-2004.

Studies on the α and ß-glucan synthase subunits in *Schizosaccharomyces pombe*. Useful targets to search for new antifungal agents. Dr. Y. Sánchez. **CICYT** (BIO2001-1663). 2002-2004.

Cooperative Iberoamerican project to search for natural and synthetic antifugal agents (PIBEAFUN). Dr. A. Durán (Spanish-Iberoamerican cooperation program: Spanish side). 2001-2004.

Study of catalytic subunits responsible for the fungal cell-wall (1-3)β-D-glucan synthesis. Useful targets for the design of new antifungal drugs. Dr. J.C. Ribas. **CICYT** (BIO2000-1448). 2001-2003.

Yeast chitin biosynthesis: a tool in the search for new antifungal agents. EUROCELLWALL. Dr. C. Roncero (Drs. A. Durán and M.H. Valdivieso included). **EC** (QLRT-1999-31537). 2001-2003.

6. THESIS AND GRADUATE WORKS

Thesis

Characterization of ß-1,3-glucanosyl-transferases from GH72 family involved in *S. pombe* cell wall remodelling. **Maria de Medina**. Univ. Salamanca. **2008**. Directors: F. del Rey and C. R. Vázquez de Aldana.

Characterization of family II chitin synthase activities from the filamentous fungus A*spergillus fumigatus.* **Cristina Jiménez**. Univ. Salamanca. **2008**. Director: C. Roncero.

Studies on the transcriptional cascade at the end of mitosis in *Schizosaccharomyces pombe.* **Mª Luisa Alonso**. Univ. Salamanca. **2007**. Directors: F. del Rey and C. R. Vázquez de Aldana.

Search for and studies on new effectors on the Cdc42p GTPase from *S. pombe*. **Sergio Rincón**. University of Salamanca. **2007**. Director: P. Pérez.

Characterization of *SWM1* and *CDC15*, two genes envolved in the regulation of *Saccharomyces cerevisiae* cell cycle. Relationship with morphogenesis. **Eva P. Hernando**. Univ. Salamanca. **2007**. Directors: F. del Rey and C. R. Vazquez de Aldana.

Function and regulation of Rgf3p during the process of cytokinesis in *Schizosaccharomyces pombe.* **Virginia Tajadura.** Univ. Salamanca. **2007**. Director: Y. Sánchez. Doctorate extraordinary mention

Characterization of genes involved in biosynthesis and degradation of α(1,3)-D-glucan from *Schizosaccharomyces pombe*. **Ignacio García**. Univ. Salamanca. **2006**. Director: Y. Sánchez.

Role of Chs2p in *Schizosaccharomyces pombe* cytokinesis. **Rebeca García**. Univ. Salamanca. **2006**. Director: Mª H. Valdivieso.

Characterization of Bgs1p and Bgs4p: two essential proteins involved in the biosynthesis of ß(1-3)-D-glucan from *Schizosaccharomyces pombe*. **Juan C. García-Cortés**. Univ. Salamanca. **2006**. Directors: J. C. Ribas and A. Durán. Doctorate extraordinary mention

Regulation of chitin synthase activity in yeast. **María Sanz**. Univ. Salamanca. **2005**. Director: C. Roncero. Doctorate extraordinary mention

Graduate Works

Role of *dni2*$^{+}$ in *Schizosaccharomyces pombe* mating. **José A. Clemente**. School of Biology. Univ. Salamanca. **2006**. Director: Mª H. Valdivieso.

Characterization of *rgf1+* and *rgf2+* genes as possible regulators of β-glucan biosynthesis in *Schizosaccharomyces pombe*. **Patricia García**. School of Biology. Univ. Salamanca. **2005**. Director: Y. Sánchez.

Study of *rho5*$^{+}$ gene from the fission yeast *Schizosaccharomcyes pombe*. **Sergio Rincón**. School of Biology. Univ. Salamanca. **2004**. Directors: P. Pérez and B. Santos.

Characterization of r*gf3*$^{+}$: regulator of Rho1p in *Schizosaccharomyces pombe*. **Virginia Tajadura**. School of Biology. University of Salamanca. **2004**. Director: Y. Sánchez.

Preliminary characterization of members of the α (1,3) glucan synthase family in *Schizosaccharomyces pombe*. **Ignacio García**. School of Biology, Univ. Salamanca. **2003**. Director: Dr. Y. Sánchez.

Cloning and characterization of *chs2*$^{+}$ gene from *Schizosacchaormyces pombe*. **Rebeca Martin**. School of Biology, Univ. Salamanca. **2003**. Director: Dr. Mª H. Valdivieso.

6. OTHER RELEVANT ACTIVITIES

"Research group of excellence" (reference GR231) of the Regional Government ("Junta de Castilla y León") "Cell wall and morphogenesis in yeast" IMB group. Grant periods: 2005-2007/2008-2010.

Involvement in the Ph. D. graduate program untitled "Molecular Microbiology and Genetics" organized by the Department of Microbiology and Genetics of the University of Salamanca and granted from 2003-04 to 2008-09 academic courses with a quality mention (ref.: MCD2003-00118) by the Spanish Ministry of Education and Science (for more information see: (http://imb.usal.es/formacion/doctorado/index7.htm)

Organization of the "II International Conference on Molecular Mechanisms of Fungal Cell Wall Biogenesis". August -September 2003. Salamanca. Spain (for more information see: http://imb.usal.es/cw2003).

Reception of Prof. Dr. Enrico Cabib, Morphogenesis Section Chief at the Laboratory of Biochemistry and Genetics, NIDDK, National Institutes of Health, Bethesda, USA, on a sabbatical stay (2003).