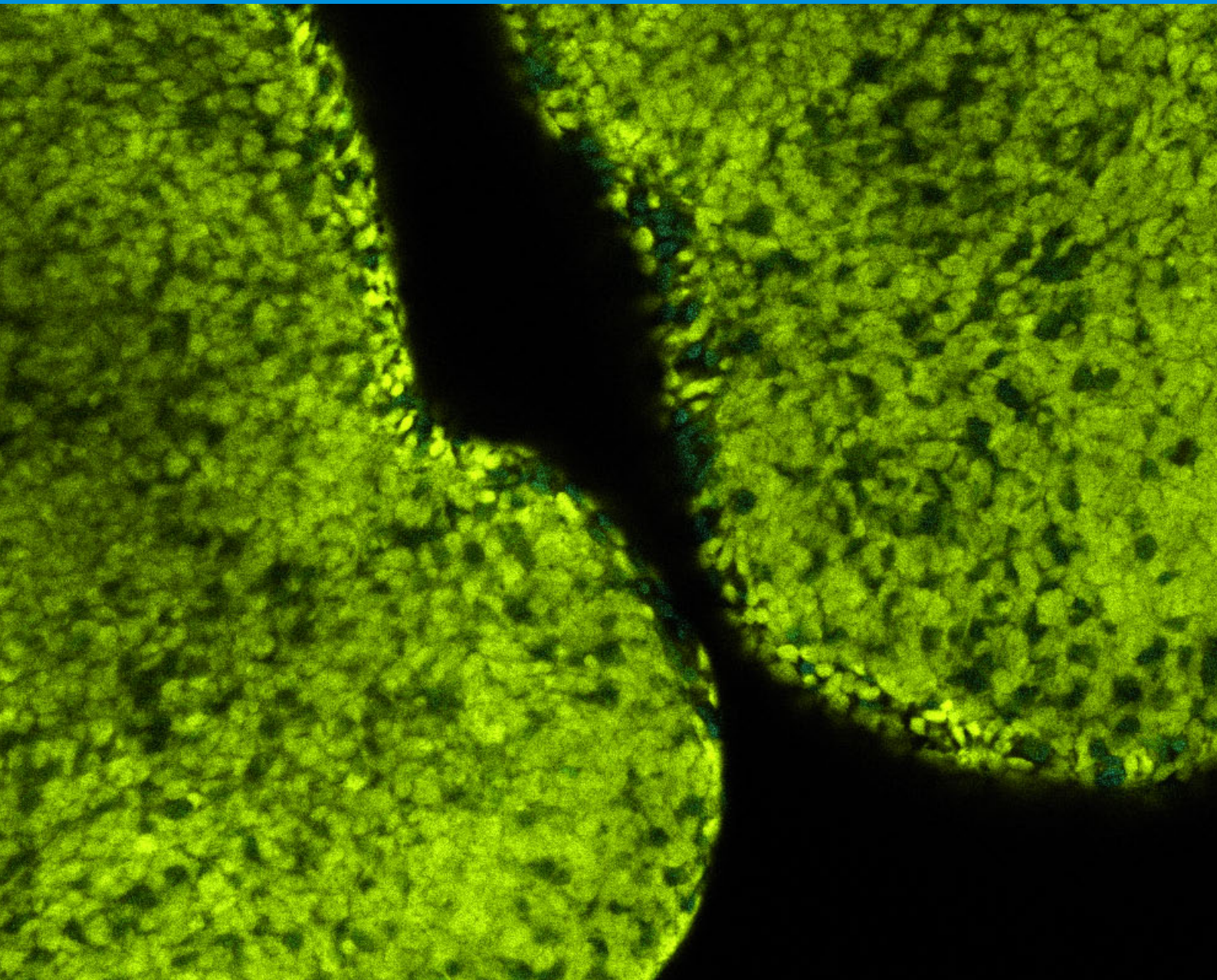
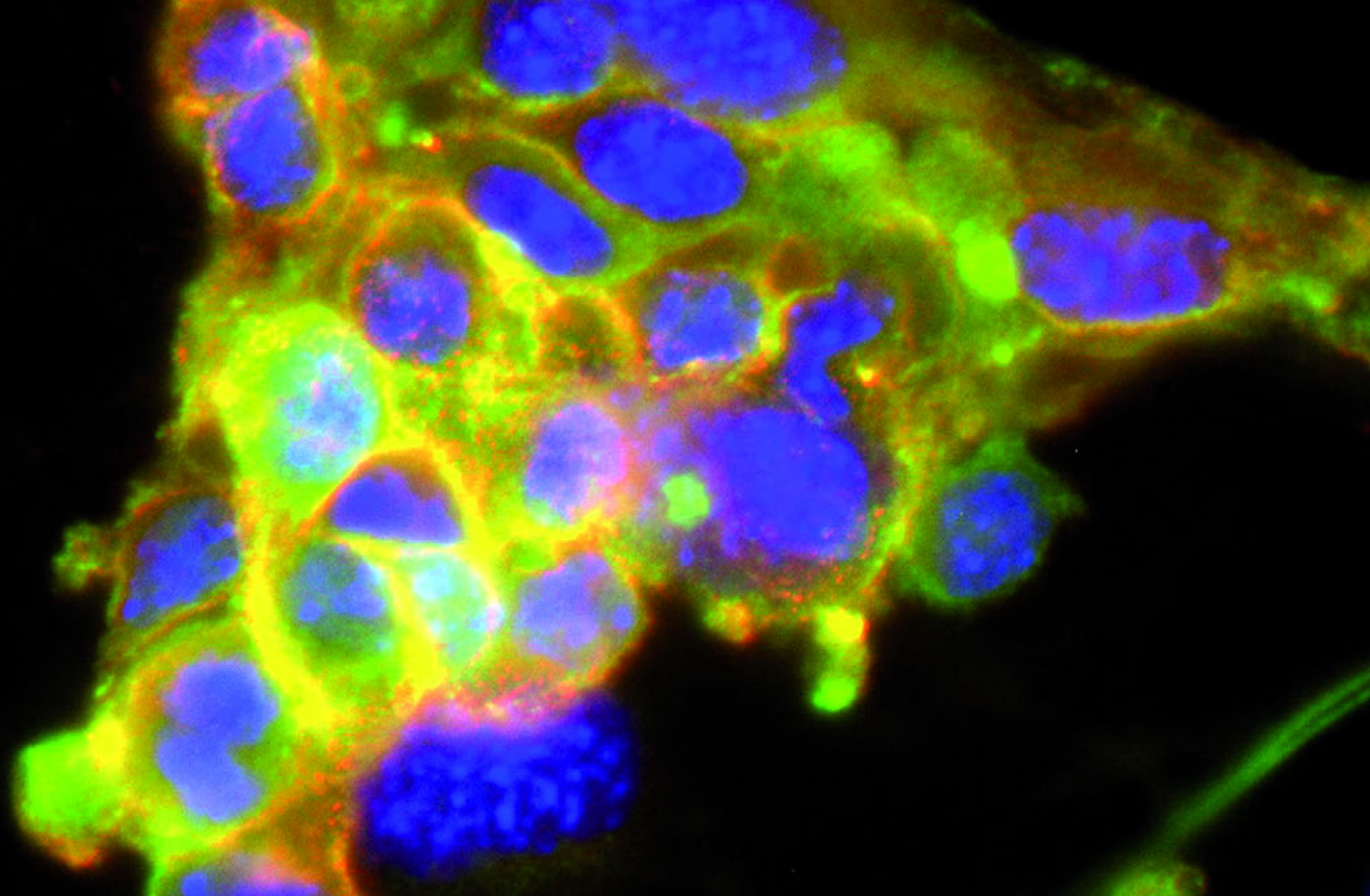


Basic Research Departments

2

Regenerative Cardiology





Basic Research Departments

2 Regenerative Cardiology

The RC department's activities center on the characterization of stem cell populations associated with cardiovascular system homeostasis, the interdependence of the cardiovascular and immune-inflammatory systems, and the roles of oxidative stress, cell cycle alterations and stem cell dysfunction in tissue aging.

DEPARTMENT DIRECTOR: *Antonio Bernad*

DEPARTMENT MANAGER: *Isabel Barthelemy*

SUPPORT SCIENTIST: *Carmen Albo*

ADMINISTRATIVE SUPPORT: *Marta Ramón*

Gene expression and genetic stability in adult stem cells



Head of Laboratory: Antonio Bernad

Research Scientists: Manuel A. González
Enrique Samper

Postdoctoral Researchers: Xonia Carvajal
Antonio Díez-Juan
Marta B. Evangelista
Silvia García
M. Paz Moreno
Isabel Moscoso
Kausalia Vijayaragavan

Predocctoral Researchers: Beatriz Escudero
J. Camilo Estrada
David Horna
Alberto Izarra
David Lara
María Tomé
Íñigo Valiente

Masters Student: Francisco M. Cruz-Uréndez

Support Scientist: Candelas Carreiro

Technicians: Vanessa Blanca
Ana Calvo
Rosa M. Carmona
Juan Carlos Sepulveda
Yaima Torres
Virginia Zorita



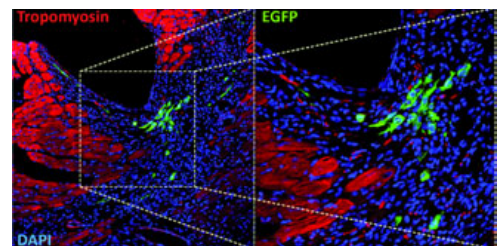
RESEARCH INTEREST

Adult stem cells (aSCs) are crucial for the maintenance of organ homeostasis throughout life. As somatic stem cells age and accumulate damage they no longer fulfill their roles efficiently. Such cells may initiate a program of senescence or apoptosis, or alternatively can become genetically unstable, posing a danger to the organism. To understand how stem cells control the processes of self-renewal and differentiation, we focus on several related areas, working mainly with mouse and human mesenchymal stem cells (MSCs) and cardiac progenitor cells (CPCs) isolated from adult hearts.

Analysis of the expression of microRNAs (miRNAs) revealed that miR-335 is significantly downregulated upon hMSC differentiation and also in other compatible differentiation models. Additionally, we found that miR-335 is upregulated in hMSCs by the canonical Wnt signaling pathway and downregulated by interferon gamma (IFN- γ), important signaling pathways that control the activation of hMSCs. These results strongly suggest that miR-335 downregulation is critical for the acquisition of reparative MSC phenotypes. In parallel studies we have analyzed the influence of ex vivo cell culture conditions on genome stability in hMSCs. Our results (Estrada et al., submitted) indicate that hMSCs are less genetically stable when cultured at high oxygen tension

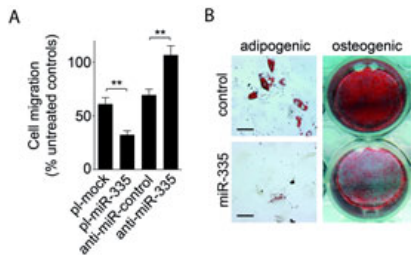
(21%), and that this instability is associated with dysregulation of several cancer-related genes and with radically altered metabolic parameters.

We have also initiated the molecular characterization of CPCs, through a comparative study of these MSC-like populations from mouse, pig and humans. Early results indicate that BMI-1 might be an important CPC marker and that the muscle-specific miRNAs miRNA-1 and miRNA-133a modulate the ability of adult and embryonic stem cells to respond to cardiomyogenic signals.



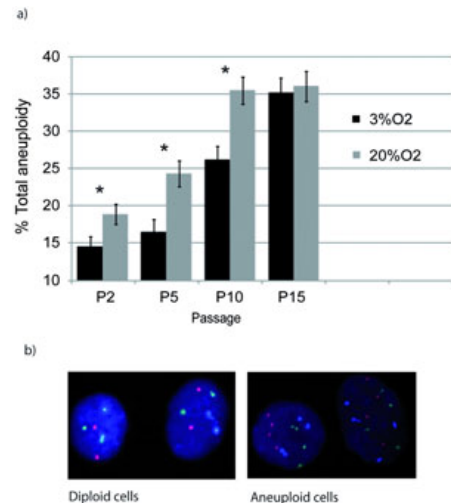
Detection of Sca-1+ CPCs transplanted into a mouse heart after acute myocardial infarction. Cells injected intramyocardially after induction of myocardial infarction by left coronary artery ligation. Sca-1+ CPCs were detected by GFP fluorescence after one week.

2 Regenerative Cardiology



Exogenous miR-335 overexpression impairs hMSC proliferation, migration and differentiation. Bone marrow-derived hMSCs were transduced with the lentiviral vectors pLV-EmGFP-MIR335 or pLV-EmGFP-mock (encoding a negative control shRNA). Transduced (GFP+) cells were purified by FACS, and used in gain-of-function studies. **(A)** hMSCs (10^4) transduced with the indicated lentiviral vector or transfected with the indicated miRNA inhibitor were used in trans-well migration assays. **(B)** hMSCs transduced with pLV-EmGFP-MIRN335 or pLV-EmGFP-mock (control) were cultured for 3 weeks in medium containing adipogenic or osteogenic factors, followed by staining with Oil Red O or Alizarin Red S, respectively.

Supraphysiological oxygen tension increases double strand breaks, chromosomal aberrations and aneuploidy in ex vivo cultured hMSCs. **(A)** Mean % aneuploidy detected in 100-200 nuclei per hMSC cell line for each oxygen concentration. Aneuploidy was detected by FISH with centromeric probes for chromosomes 8, 13, and 17. Black bars represent hMSCs grown at 3% O_2 ; gray bars represent cells grown at 20% O_2 . Growth at 3% O_2 significantly reduced the incidence of aneuploidy from passage 2 -10 ($p < 0.05$). **(B)** Representative images of hMSC nuclei hybridized with CEP probes for chromosomes 8 (red), 11 (green) and 17 (pale blue) in diploid cells grown at 3% O_2 (left panel) and in highly aneuploid cells grown at 20% O_2 cell (right panel). Nuclei are stained with DAPI (blue).



MAJOR GRANTS

- European Commission FP7. European Multidisciplinary Initiative (FP7-HEALTH -2009 CAREMI). PI, Dr. Antonio Bernad (coordinator)
- Ministerio de Ciencia e Innovación. Programa Nacional de Internacionalización de la I+D (PLE 2009/0147). Sub-project coordinator: A. Bernad
- Ministerio de Ciencia e Innovación. FIS (CP07/00306). PI: M. A. González de la Peña
- Ministerio de Ciencia e Innovación. Programa Nacional de Internacionalización de la I+D (PLE2009 2009/0112). PI: M. A. González de la Peña
- Ministerio de Ciencia e Innovación (SAF2008-02099). PI, A. Bernad
- Mantenimiento de la estabilidad genómica en células madre. Implicación en la bioseguridad en medicina regenerativa. (S-BIO-0306-2006) PI: Dr. A. Bernad (coordinator)
- Ministerio de Ciencia e Innovación. FIS RETICS (TERCEL: RD06/0010/0018). Subproject Coordinator: A. Bernad
- Comunidad de Madrid: Plan de Innovación Empresarial (CEIT06). PI: E. Samper



SELECTED PUBLICATIONS

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* Corresponding authors

García S, Bernad A, Martín MC, Cigudosa JC, Garcia-Castro J, de la Fuente R. Pitfalls in spontaneous in vitro transformation of human mesenchymal stem cells. *Exp Cell Res* (2010). 316:1648-50

Carvajal-Vergara X, Sevilla A, D'Souza SL, Ang YS, Schaniel C, Lee DF, Yang L, Kaplan AD, Adler ED, Rozov R, Ge Y, Cohen N, Edelmann LJ, Chang B, Waghay A, Su J, Pardo S, Lichtenbelt KD, Tartaglia M, Gelb BD, Lemischka IR. Patient-specific induced pluripotent stem-cell-derived models of LEOPARD syndrome. *Nature* (2010) 465: 808-12

Jalife J, Atienza F, López-Salazar B, E. Delpón, Sánchez-Quintana D, Bernad A, Almendral A. Molecular, cellular and pathophysiological mechanism of human atrial fibrillation. *Nat Clin Pract Cardiovasc Med* (2009) 6: 15-21

Gago N, Pérez-López V, Sanz-Jaka JP, Cormenzana P, Eizaguirre I, Bernad A, Izeta, A. Age-dependent depletion of human skin-derived progenitor cells. *Stem Cells* (2009) 27:1164-72.

Functional genetics of the oxidative phosphorylation system

Head of Laboratory: *José Antonio Enríquez*

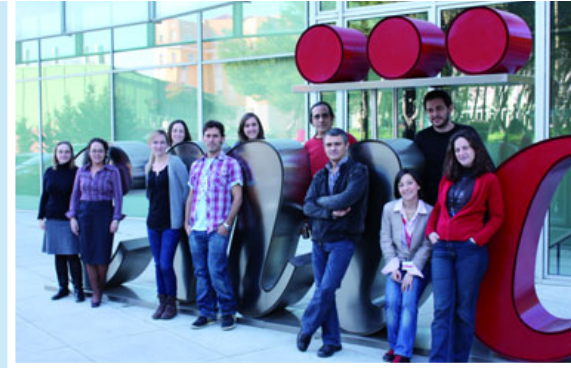
Research Scientists: *Acisclo Pérez Martos
Patricio Fernández Silva
Erika Fernández -Vizarra
Nuria Garrido Pérez
Pilar Bayona Bafaluy*

Postdoctoral Researchers: *Carmen Colás Esteban
Ester Perales Clemente
Patricia Meade Huerta
Raquel Moreno Loshuertos*

Predocctoral Researchers: *Ricardo Marco Lázaro
Adela María Guaras Rubio
Ana Latorre Pellicer
Esther Lapuente Brun
Elena de Tomás Mateo*

Support Scientists: *M^a Concepción Jiménez Gómez
Nieves Movilla Meno
Marta Roche Molina*

Visiting Scientists: *Eduardo Balsa Martinez
Sara Cogliati*

**RESEARCH INTEREST**

Disorders of the mitochondrial oxidative phosphorylation (OXPHOS) system are among the most common inherited metabolic disorders, affecting an estimated 1 in every 5000 live births. The mitochondrial OXPHOS system comprises the four respiratory chain complexes (complexes I, II, III and IV) and ATP synthase (complex V), and is the major source of ATP in eukaryotic cells. The mtDNA mutations associated with the clinical phenotypes of these diseases fall into three main categories: 1) Point mutations affecting either protein synthesis genes (rRNA and tRNA) or mtDNA-encoded structural OXPHOS subunits; 2) Rearrangements, which can be single or multiple deletions or partial duplications; 3) Depletions, in which the amount of mtDNA is significantly reduced. Although these mtDNA defects are seldom associated solely with cardiomyopathy, they have serious effects on cardiac tissue because OXPHOS-derived ATP is essential for the heart's contractile activity. After encephalomyopathy, predominantly cardiac hypertrophy, is the most common pathology associated with mtDNA point mutations.

We use a range of approaches to investigate the role of the OXPHOS system in health and disease. One reason for the current limited knowledge in this area is that established models of electron transport chain organization are flawed. To address this, we are implementing high-throughput strategies to catalogue the set of the genes whose products participate in the biogenesis and regulation of the OXPHOS system (which we call the OXPHOME). We are also determining the factors that regulate the structural organization of the electron transport chain and the role that this superstructural organization plays in the production of reactive oxygen species (ROS). This area is linked to our interest in the role of ROS as mitochondrial second messengers and to our aim to deconstruct, in cellular models, the mammalian OXPHOS system into its functional components (electron transport, proton pumping and ATP synthesis).

Cardiovascular related risks of obesity

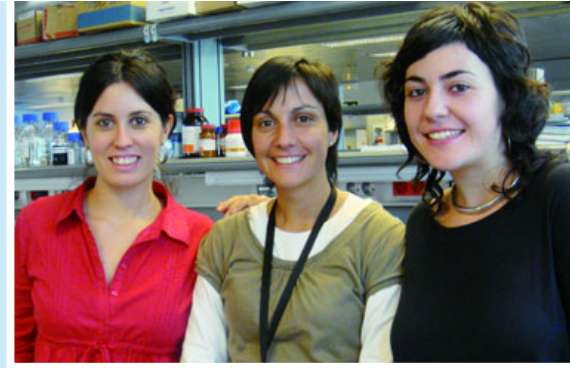


Head of Laboratory: *Beatriz G. Gálvez*

Masters Students: *Aurora Bernal
María Fernández*

Technician: *Nuria San Martín*

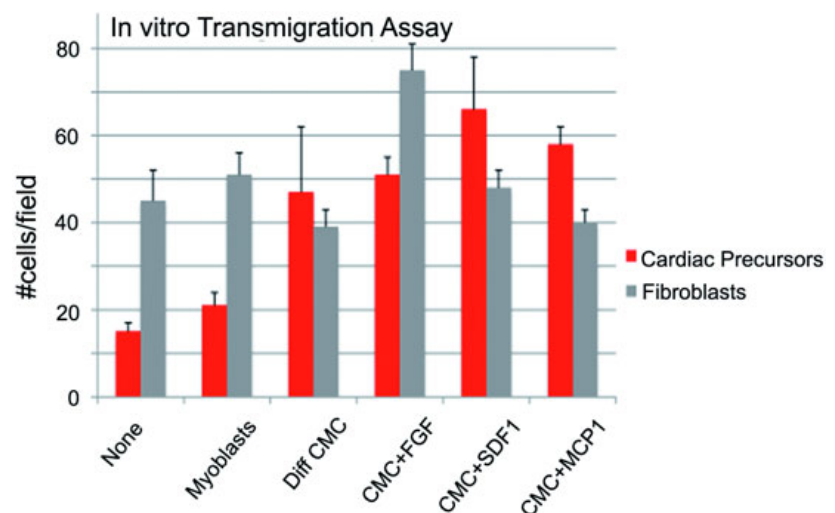
Visiting Scientist: *Claudia Cordova*



RESEARCH INTEREST

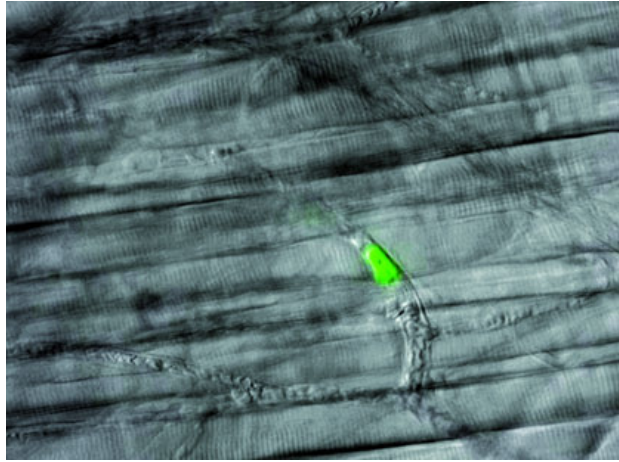
Efficient delivery of cells to heart regions is a major problem for cell therapy. Our research focuses on improving migration of mouse and human cardiac precursors to damaged heart tissue. We have found that cardiac precursors are induced to transmigrate through the endothelium by cytokines and other factors released by cardiomyocytes, among which SDF-1 is the most potent. In vivo, unstimulated GFP-tagged cardiac precursors are delivered through the femoral artery to regenerating damaged heart tissue of normal mice and mice subjected to coronary artery ligation (CAL). Quantitative PCR indicates that in vivo homing of unstimulated cardiac precursors, but pretreatment with SDF-1 increases homing threefold. Furthermore, transmigration and homing is also

increased by transient expression of various surface molecules. After combined pretreatment with cytokines and surface molecules, around 50% of cardiac precursors home directly to damaged heart after intra-artery injection in CAL-treated mice. We are conducting long term experiments to assess the capacity of these modified cardiac precursors to regenerate the surface of the ventricle wall after injection into the left ventricular chamber. By defining the requirements for efficient homing of cardiac precursors to damaged heart, we aim to provide tools that will optimize cell therapy protocols for the treatment of cardiovascular diseases.



Transwell assay: Migration of stimulated cardiac precursors across the endothelium

2 Regenerative Cardiology



Intra-vital microscopy: SDF-1-stimulated GFP-tagged cardiac precursor crossing the endothelium.



MAJOR GRANTS

- Ministerio de Ciencia e Innovación (RYC2009-04669)
- Ministerio de Ciencia e Innovación (SAF2010-15239)



SELECTED PUBLICATIONS

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[Galvez BG](#), [Martín NS](#), Salama-Cohen P, Lazcano JJ, Coronado MJ, Lamelas ML, Alvarez-Barrientes A, Eiró N, Vizoso F, Rodríguez C. **An adult myometrial pluripotential precursor that promotes healing of damaged muscular tissues.** *In Vivo* (2010) 24 :431-41

Koyanagi M, Iwasaki M, Rupp S, Tedesco FS, Yoon CH, Boeckel JN, Trauth J, Schütz C, Ohtani K, Goetz R, Iekushi K, Bushoven P, Momma S, Mummery C, Passier R, Henschler R, Akintuerk H, Schranz D, Urbich C, [Galvez BG](#), Cossu G, Zeiher AM, Dimmeler S. **Sox2 transduction enhances cardiovascular repair capacity of blood-derived mesoangioblasts.** *Circ Res* (2010) 106: 1290-302

Barbuti A, [Galvez BG](#), Crespi A, Scavone A, Baruscotti M, Brioschi C, Cossu G, DiFrancesco D. **Mesoangioblasts from ventricular vessels can differentiate in vitro into cardiac myocytes with sinoatrial-like properties.** *J Mol Cell Cardiol* (2010) 48: 415-23

Stem cell aging



Head of Laboratory: Susana González

Postdoctoral Researcher: Lorena Arranz

Predoctoral Researchers: Antonio Herrera Merchán
Patricia Giraldo

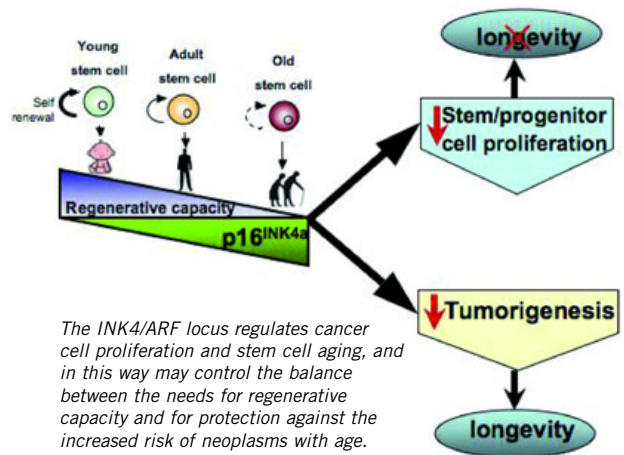


RESEARCH INTEREST

The INK4b-ARF-INK4a locus encodes three tumour suppressors, p15INK4b, ARF, and p16INK4a. Together, these factors constitute one of the most important sources of cancer protection in mammals, equalled in importance only by p53. These tumour suppressors have taken on additional importance in the light of recent evidence that at least one product of the locus, p16INK4a, also contributes to the decline in the replicative potential of self-renewing cells with age. Thus, on the one hand, p16INK4a promotes longevity through its action as a potent tumour suppressor, while on the other hand the increased expression of p16INK4a with age reduces stem and progenitor cell proliferation, ultimately reducing longevity. In other words, p16INK4a appears to balance the need to prevent cancer against the need to sustain regenerative capacity throughout life. These observations suggest the provocative but unproven notion that mammalian aging results in part from the effectiveness of tumour suppressor proteins at preventing cancer.

Our group is investigating the role and molecular regulation of the INK4b-ARF-INK4a locus in the context of self-renewal, proliferation and aging of hematopoietic stem cells in vitro and in vivo, with planned extension of these studies

to cardiac stem cells. In parallel, we are developing tools for the study of the genetic and epigenetic mechanisms that regulate stem cells, and how these unique cells differentiate from a pluripotent to a more restricted state.



MAJOR GRANTS

- Human Frontier Science Program Organization (HFSP). Career Development Award
- Ministerio de Ciencia e Innovación. FIS (PI060627)
- Ministerio de Ciencia e Innovación (SAF2010-15386)



SELECTED PUBLICATIONS

Herrera-Merchan A, Cerrato C, Luengo G, Dominguez O, Piris MA, Serrano M, González S. miR-33-mediated downregulation of p53 controls hematopoietic stem cell self-renewal. *Cell Cycle* (2010) 9: 3277-85

Daroca PM, Herrera-Merchán A, González S. Insights into stem cell aging. *Nat Rev Cardiol (CNIC Edition)* (2010) 7: 11-5

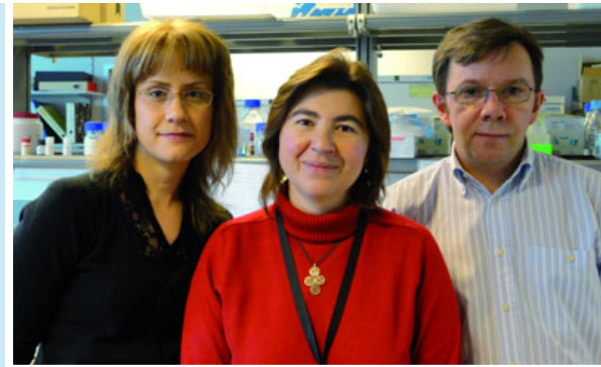
Stem cell signaling



Head of Laboratory: *Kenneth J. McCreath*

Research Scientist: *Ana M. Cervera*

Postdoctoral Researcher: *Sandra Espada*



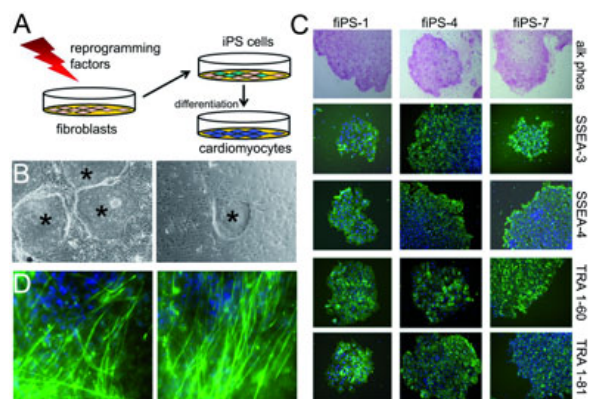
RESEARCH INTEREST

The prevailing view of mitochondria as bioenergetic facilitators has been extended by the observations that these organelles play critical roles in many cellular events. Using embryonic stem (ES) and induced pluripotent stem (iPS) cells as in vitro models we are investigating the participation of mitochondria in the maintenance of stem cell pluripotency and the capacity for differentiation. We recently showed that mitochondrial ROS, produced in high glucose cultures, are required for the differentiation of ES cell-derived cardiomyocytes. Building on these results, we are examining the regulation of microRNA (miRNA) expression during ES cell differentiation, and we are characterizing several miRNAs that are differentially expressed upon ROS depletion. In addition, we are devising protocols for the directed differentiation of human iPS cells to cardiac progenitor populations, in the hope that these cells can be used in a therapeutic context. Moreover, we are examining the possibility that stem cells derived from patients with congenital defects could provide valuable models of cardiovascular disease.

Tissue hypoxia, during cardiovascular disease, leads to increased levels of mitochondrial metabolites. Using novel loss-of-function mouse models, we are currently examining the

potential of these metabolites to act as signaling molecules for cellular restoration.

Together, we expect these approaches will aid in the understanding of mitochondrial participation during both cardiovascular development and disease.



Reprogramming of fibroblasts to induced pluripotent stem (iPS) cells. (A) Schematic representation of the reprogramming process and subsequent differentiation of iPS cells to cardiomyocytes. (B) iPS cells in culture after fibroblast reprogramming. (C) Undifferentiated surface marker expression in iPS cells. (D) Serum-driven differentiation of iPS cells leads to cardiomyocyte formation, revealed by cardiac α -actinin staining (green).



MAJOR GRANTS

Ministerio de Ciencia e Innovación (SAF2009-07965)



SELECTED PUBLICATIONS

Luna-Crespo F, Sobrado VR, Gomez L, Cervera AM, McCreath KJ. Mitochondrial Reactive Oxygen Species Mediate Cardiomyocyte Formation from ES Cells in High Glucose. *Stem Cells* (2010) 28: 1132-1142

Cervera AM, Bayley J-P, Devilee P, McCreath KJ. Inhibition of succinate dehydrogenase dysregulates histone modifications in mammalian cells. *Mol Cancer* (2009) 8:89

Hernandez C, Santamatilde E, McCreath KJ, Cervera AM, Diez I, Ortiz-Masia D, Martinez N, Calatayud S, Esplugues JV, Barrachina MD. Induction of trefoil factor (TFF) 1, TFF2 and TFF3 by hypoxia is mediated by hypoxia inducible factor-1: implications for gastric mucosal healing. *Br J Pharmacol* (2009) 156: 262-272

Transcriptional regulation of oxidative stress protection systems



Head of Laboratory: *María Monsalve*

Postdoctoral Researchers: *Nieves García-Quintáns*
Alberto Tierrez

Predocctoral Researchers: *Yolanda Olmos*
Cristina Sánchez
Brigitte Wild

Undergraduate Students: *Sofía Cabezudo*
Javier Laso



RESEARCH INTEREST

Our group studies the transcriptional mechanisms that regulate oxidative stress protection in mammals. Metabolic dysfunction and associated mitochondrial oxidative stress are emerging as primary risk factors for several major diseases, and a precise understanding of the mechanisms that control ROS detoxification will therefore be crucial for the development of new treatment strategies. We research the transcription factors involved in the regulation of the ROS detoxification system and the impact this regulation has on human diseases, with particular emphasis on those affecting the cardiovascular system.

Our work over the last year focused on two key areas:

1.- Modulation of angiogenesis by ROS. We have found that when the cells lose their cell-cell contacts and produce nitric oxide, this downregulates PGC-1 α levels via activation of the PI3K/AKT pathway and inactivation of the transcription factor FoxO3. The outcome is increased mitochondrial superoxide production, which is necessary for nitric oxide induced cell migration during the initial phase of angiogenesis.

2.- ROS-mediated DNA damage triggered by cell cycle arrest. The mechanisms linking ROS levels to the control of the cell cycle are still very poorly understood. We have identified the genotoxic sensor TLS (translocated in liposarcoma) as a key regulatory component of the transcriptional complex that modulates oxidative stress protection systems via interaction with PGC-1 α .

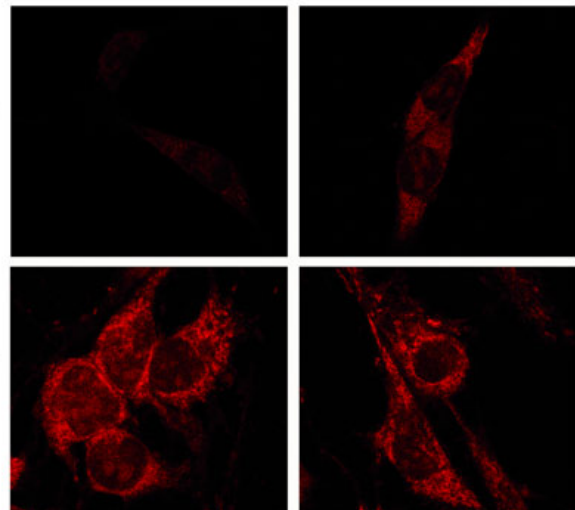
The nitric oxide/cGMP pathway cannot regulate mitochondrial ROS production in the absence of peroxisome proliferator activated receptor γ -coactivator 1 α (PGC-1 α). MitoSOX Red labeling reveals mitochondrial superoxide levels in wild-type (PGC-1 $\alpha^{+/+}$) and PGC-1 α knockout (PGC-1 $\alpha^{-/-}$) mouse lung endothelial cells treated with 8-Br-cGMP.

PGC-1 $\alpha^{+/+}$

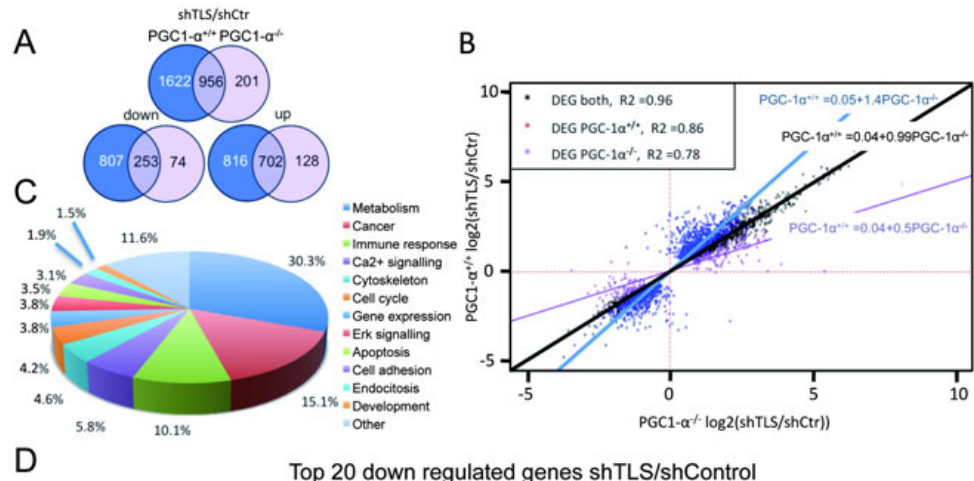
PGC-1 $\alpha^{-/-}$

Vehicle

cGMP



2 Regenerative Cardiology



D Top 20 down regulated genes shTLS/shControl

Gene	Protein	PGC1-α ^{+/+} Log ₂ (shTLS/shCtr)	Adj p value	PGC1-α ^{-/-} Log ₂ (shTLS/shCtr)	Adj p value
Cldn2	claudin-2	-4.7625	0.004847	-3.6807	0.022208
Hsd3b5	3-beta-hydroxy-5-ene steroid dehydrogenase	-4.1193	0.018085	-3.3091	0.060249
Anks1b	AIDA-1	-4.0950	0.000960	-2.2200	0.032002
Ubie	Ubiquinone	-3.5113	0.001586	-2.9366	0.005086
C23003516Rik	unknown	-3.4785	0.011074	-2.6545	0.046782
Miph	melanophilin1	-3.2921	0.006520	-3.5228	0.005622
Xpnp2	X-prolyl aminopeptidase	-3.2513	0.020283	0.3243	0.812333
Gzmd	granzyme D	-3.2398	0.038417	-1.0964	0.462563
9930111J21Rik	unknown	-3.1368	0.040939	-0.8222	0.579582
9530096D07Rik	unknown	-3.1364	0.031196	-1.4899	0.276342
NAP034039-1	unknown	-3.1317	0.016547	-1.7915	0.141157
TC1600999	unknown	-3.0842	0.015944	-2.5310	0.050064
LOC620079	unknown	-3.0761	0.023329	0.5971	0.634634
Lin54	lin-54 homolog (C. elegans)	-3.0692	0.021766	0.7468	0.133538
BC106179	unknown	-3.0238	0.014602	-2.6104	0.038926
Mrgprb3	MAS-related GPR, member B3	-3.0181	0.018809	-2.8091	0.037460
Ptscr3	Phospholipid scramblase 3	-3.0156	0.003453	-1.1615	0.101653
Entpd8	ectonucleoside triphosphate diphosphohydrolase 8	-2.9935	0.004123	-1.6588	0.068656
Il3	interleukin-3	-2.9876	0.042027	0.0169	0.992510
Anp32a	acidic nuclear phosphoprotein 32 family member A	-2.9588	0.029677	-1.2300	0.332180

Top 20 up regulated genes shTLS/shControl

Gene	Protein	PGC1-α ^{+/+} Log ₂ (shTLS/shCtr)	Adj p value	PGC1-α ^{-/-} Log ₂ (shTLS/shCtr)	Adj p value
Sox12	Transcription factor SOX	9.5002	0.326 10 ⁻³	9.1412	0.411 10 ⁻³
Cxnc6	TET1	6.9569	0.097 10 ⁻³	6.5895	0.134 10 ⁻³
Cck	Cholecystokinin	6.8334	0.123 10 ⁻³	0.4568	0.781714
A_52_P877097	unknown	6.0632	0.037 10 ⁻³	6.1319	0.030 10 ⁻³
Olfir738	olfactory receptor 738	6.0477	0.016 10 ⁻³	6.1156	0.013 10 ⁻³
Fndc8	fibronectin type III domain containing 8	5.9647	0.207 10 ⁻³	6.2843	0.127 10 ⁻³
TC1719751	unknown	5.8899	0.063 10 ⁻³	5.3262	0.119 10 ⁻³
Xcr1	Chemokine XC receptor 1	5.8869	0.010 10 ⁻³	6.0151	0.006 10 ⁻³
Gtbp3	GTP binding protein 3	5.8698	0.037 10 ⁻³	-0.4511	0.548513
Unc5d	unc-5 homolog D	5.8242	0.505 10 ⁻³	5.5297	0.710 10 ⁻³
Tbc1d2	TBC1 domain family, member 21	5.7955	0.026 10 ⁻³	5.7119	0.027 10 ⁻³
Arl10	ADP-ribosylation factor-like 101	5.7743	0.026 10 ⁻³	-1.0458	0.105760
Asb7	ankyrin repeat and SOCS box-containing protein 7	5.7627	0.016 10 ⁻³	-1.0685	0.140550
AK036326	unknown	5.5209	0.044 10 ⁻³	5.7643	0.030 10 ⁻³
CA481501	unknown	5.5100	0.318 10 ⁻³	4.8868	0.975 10 ⁻³
E230015807Rik	unknown	5.5002	0.010 10 ⁻³	5.4391	0.009 10 ⁻³
Adpnh1	ADP-ribosylhydrolase like 1	5.4203	0.016 10 ⁻³	5.6044	0.013 10 ⁻³
Terc	telomerase RNA component	5.3626	0.016 10 ⁻³	-0.6817	0.611241
B230396O12Rik	unknown	5.3510	0.016 10 ⁻³	5.0655	0.020 10 ⁻³
A_51_P516033	unknown	5.2432	0.065 10 ⁻³	5.3998	0.043 10 ⁻³

TLS transcriptional activity is dependent on PGC-1α. Whole genome expression and function analysis of primary PGC-1α^{+/+} and PGC-1α^{-/-} hepatocytes infected with shTLS or control adenovirus.

MAJOR GRANTS

- Ministerio de Ciencia e Innovación (SAF2009-07599)
- Ministerio de Ciencia e Innovación. CONSOLIDER Project (CSD2007-00020)

SELECTED PUBLICATIONS

Monsalve M, Olmos Y. The complex biology of FoxO. *Current Drug Targets* (accepted)

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Valle I, Olmos Y, Borniquel S, Tierrez A, Soria E, Lamas S and Monsalve M. Foxo3a is both upstream and downstream of PGC-1α in the induction of oxidative stress genes. *J Biol Chem* (2009) 284: 14476-84.

Nuclear receptor signaling



Head of Laboratory: Mercedes Ricote

Postdoctoral Researchers: Piedad Menéndez
Tamás Röszer
Lucía Fuentes

Predoctoral Researchers: Daniel Alameda
Marta Cedenilla

Technician: Vanessa Nuñez



RESEARCH INTEREST

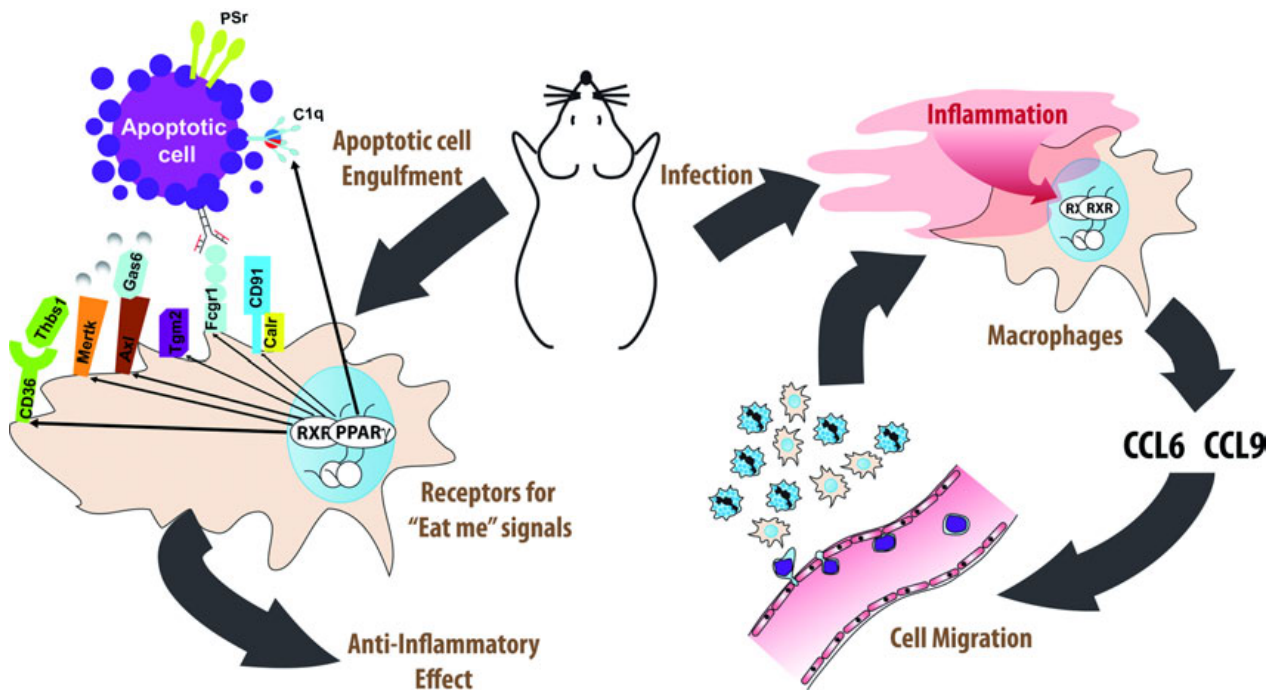
Nuclear hormone receptors (NRs) are important regulators of metabolism and homeostasis, and participate in a wide variety of biological processes including vascular and cardiac function, lipid metabolism, toxin clearance, and inflammation. Work by our group is contributing to the definition of the role of NRs in the immune response, with special emphasis on the function of NRs in tissue inflammation and the differentiation of myeloid cells from stem cell to macrophage. We are interested in the role of RXRs (retinoid X receptors) in chronic inflammatory diseases (autoimmunity, atherosclerosis and diabetes) and the homeostasis of adult stem cells.

We recently found that myeloid-specific RXR α knockout mice exhibit impaired recruitment of leukocytes to sites of inflammation and lower susceptibility to sepsis. These mice moreover develop glomerulonephritis and autoantibodies to

nuclear antigens, resembling the nephritis seen in human systemic lupus erythematosus. These findings demonstrate that RXR plays a key role in the regulation of innate immunity and represents a potential target for immunotherapy of sepsis and autoimmunity. These defects eventually lead to the development of insulin resistance and cardiac hypertrophy, and we are currently trying to understand how the lack of RXRs may be involved in the development of these conditions.

Our research into adult stem cells addresses the role of NRs in the mobilization of hematopoietic stem and progenitor cell trafficking to sites of inflammation in mice. We have generated hematopoietic-specific PPAR γ and RXR α , β -knockout mice, and our aim is to define the role of these nuclear receptors in tissue repair and regeneration.

2 Regenerative Cardiology



Immunomodulatory functions of RXR: two faces of the same receptor RXR can form heterodimers with PPAR γ (left) and regulate the expression of cell surface receptors that recognize the "eat me" signals from apoptotic cells. Efficient uptake of apoptotic cells induces an anti-inflammatory macrophage phenotype. Absence of this regulatory pathway (for example in mice lacking macrophage PPAR γ or RXR α) leads to accumulation of apoptotic debris and evokes autoimmunity. RXR homodimers (right) are essential for the expression of chemokines and thus contribute to proper migration of macrophages to sites of inflammation.



MAJOR GRANTS

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SELECTED PUBLICATIONS

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