Laboratory for Cell Reprogramming

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Keywords

Cell reprogramming, iPSCs, stem cells, ooctye, pluripotency, menstrual blood-derived stromal cells, neurodegenerative disease, disease modeling

Research Lines

✓ Somatic cell reprogramming analysis. Identification of new factors involved in the process and analysis of pathways involved.
✓ Disease in a dish. Use of cell reprogramming for neurodegenerative disease modeling

Scientific Activity

Our long-term goal is to provide new insights into cellular reprogramming by analyzing molecular pathways, and identifying new factors that could play an important role in cell reprogramming, here is specially important to mention we use the oocyte as source of information to study pluripotency acquisition. The results of our work will inform the development of safe and efficient cell reprogramming protocols to be tested in pre-clinical and clinical models of human disease.

Cell reprogramming is also used in our laboratory for neurodegenerative disease modeling. Whether or not a disease can be treated often depends on whether we can gain a good understanding of its basic biology. Disease modelling using iPSC technology allows scientists to explore how a disease works in the laboratory, to search affected pathways and alternative treatment.

Research lines:

✓ **Somatic cell reprogramming analysis. Identification of new factors involved in the process and analysis of pathways involved**

Cellular reprogramming, briefly defined as the transformation of a specialized cell into another of a different type. When referring to cellular reprogramming in the context of induced pluripotent cells (iPSCs) we can distinguish a first step called dedifferentiation, where cells reach a pluripotent stage and subsequently induced to differentiate into specific cell types. This phenomenon was described for the first time in 2007 by two laboratories simultaneously, Prof. S. Yamanaka and Prof. J.Thomson, showing human fibroblasts transformation to pluripotent cells (iPSCs) through ectopic expression of four transcription factors (OCT4, SOX2, KLF4 and c-Myc or OCT4, SOX2, NANOG and LIN28 respectively).

Although theoretically this is a “simple” protocol, cellular reprogramming is still a very inefficient process and more importantly, the molecular mechanisms governing the transformation of a somatic cell into an iPSC are still not completely understood.

The process by which a somatic cell acquires a pluripotent state is an epigenetic phenomenon, we and others study the specific molecular mechanisms involved. The evidence provided by our research supports the idea that studying the genes and gene products present in the oocyte (more specifically the unfertilized metaphase II oocyte) can help us understand how pluripotency is acquired in somatic cells.

Cell reprogramming is also associated with cellular transdifferentiation, that is a cell from one differentiated lineage is transformed into a different differentiated cell e.g. from fibroblast to sperm without having to be go through the process of dedifferentiation first. While theoretically more simple, this approach is inefficient and is still at stages of development that are even more primitive than iPSC technologies. Nonetheless it has great appealing for future applications in cell therapy due to its safety, and therefore must be pursued in parallel with more established strategies. .

✓ **Disease in a dish. Use of cell reprogramming for neurodegenerative disease modeling**

Induced pluripotent stem cells (iPSCs) use is particularly useful for the study of rare diseases, specifically in neurodegenerative diseases. Nervous tissue samples from patients are rarely accessible and animal models, often do not recapitulate all characteristic of the disease.

The discovery that somatic cells from patients affected by neurological disorder can be reprogrammed to a pluripotent state (iPS cells), and once reprogrammed, these cells can expand and differentiate into specific populations of neurons, opened a promising field for research and understanding the molecular and cellular basis of these abnormalities and the development of specific drugs.

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Our short term goal is to generate iPSCs and specific cell types affected in different neuropathies such as Ataxias, multiple sclerosis, West syndrome and Huntington disease among others, and to develop in vitro models in which perform functional assays to uncover altered cellular pathways that may explain the origin of the specific pathological states. Through scientific collaborations we anticipate the discovery of new drug targets that may enable the development of pharmacological interventions.

Collaborations

- **Michigan State University** (USA). Jose B. Cibelli, cell reprogramming and cell nuclear transfer.
- **Houston Methodist Hospital** (USA). Phillip Horner. Demyelinating diseases
- **RADyTTA** (Red Andaluza de diseño y traslación de terapias avanzadas) Cellular Production and Reprogramming Unit (UPRC, Seville). Hemorrhagic cerebrospinal fluid neural stem cells study and Spinal Cord Injury cell therapy..
- **Virgen del Rocío Hospital** (Sevilla, Spain). Javier Marquez. Spinal cord injury cell therapy.
- **GENyO, Bioinformatic Unit** (Dr. Pedro Carmona). Analysis of pluripotent specific cell signatures. .
- **CABIMER, Andalusian Center for Regenerative Medicine** (Sevilla, Spain). Manuel A. Dolado. Friedreich Ataxia cell transplantation modeling.
- **Universite Claude Bernard Lyon** (France). Jordane Biarc. Proteomic analysis of secreted factors.

Research Projects in the last 5 years

- Multidisciplinary action for Rare disease and personalized medicine. Huntington disease modeling. AMER (FEDER-INNTERCONECTA R+D statal program) (2013-2016). PIs: Jose Cibelli y Elena González Muñoz
- Generation of cellular models of multiple sclerosis disease using the oligodendrocytic cell types obtained by autologous somatic cell reprogramming. Fundación Genzyme (2015-2017). PI: Elena Gonzalez Muñoz
- Molecular and epigenetic study of adult somatic cell reprogramming, and application in disease modeling for potential therapies. Spanish Economy Ministry. Associated project to “Ramón y Cajal” program (2016-2021). PI: Elena Gonzalez Muñoz
- Adult somatic cell epigenetic reprogramming: New factors involved. SAF2015-66105-R. Spanish Economy Ministry. Project I+D+I, National program for research, development and innovation (2016-2020). PI: Elena González Muñoz
- The pluripotent signature of the iPSCs: factors involved for their application in regenerative medicine and disease models (UMA18-FEDERJA-107). Consejería General de Universidades, Investigación y Tecnología. Junta de Andalucía. Programa Operativo FEDER Andalucía 2014-20. 2020-2022. IP: Mª Elena González Muñoz

Publications in the last 5 years

- ✓ Sanzhez-Mata A., Ferez-Gomez A., Gonzalez-Munoz E. Protocol to Reprogram Human Menstrual Blood-Derived Stromal Cells to Generate AOX15-iPSCs. STAR Protocols 2020 Dec 18 1(2):100183. https://doi.org/10.1016/j.xpro.2020.100183
- ✓ Lopez-Caraballo, L.; Martorell-Marugan, J.; Carmona-Sáez, P.; Gonzalez-Munoz, E*. (*corresponding author). iPS-Derived Early Oligodendrocyte Progenitor Cells from SPMS Patients Reveal Deficient In Vitro Cell Migration Stimulation. Cells 2020 Jul 29;9(8):1803. doi: 10.3390/cells9081803.
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Publications in the last 5 years

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- ✓ Gonzalez-Muñoz E*, Cibelli JB.* (*co-corresponding authors). Somatic cell reprogramming informed by the oocyte. Stem Cells Dev. 2018 Jul 1;27(13):871-887. doi: 10.1089/scd.2018.0066

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Patents

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