SELF-ORGANIZATION IN BIOLOGICAL SYSTEMS
NATALIA SÁNCHEZ

PROFILE

Natalia Sanchez de Groot has a PhD in Biotechnology from the Autonomous University of Barcelona. Her thesis won the UAB extraordinary prize. She did two internships at the Netherlands Institute for Systems Biology (the Netherlands, MICINN FPI scholarship) and at the Institute of Chemical and Biological Technology (Portugal, FEBS short-term scholarship). She has worked for five years at the prestigious Laboratory of Molecular Biology in Cambridge (England), which has hosted 12 Nobel laureates. During that time, she was funded with the FEBS long-term scholarships and the IEF Marie Curie, and her work was awarded the MRC Centenary Award. Then she worked for five years at the Centre for Genomic Regulation in Barcelona. In 2022, she won the Spanish L'OREAL – UNESCO for Women in Science prize. Currently, she enjoys a Ramón y Cajal grant and an I+D+i Project of Plan Estatal.

RESEARCH

RESEARCH INTERESTS

In Nature, we can find multiple examples of patterns and organized arrangements that have been exploited for biological purposes by living beings since their origin. In this context, with the aim to guarantee the correct development of biochemical reactions and biological processes, cells require the spatiotemporal organization of their components.

Cells achieve this organization through mechanical actions such as active transport and membrane isolated compartments but also by exploiting the physicochemical properties of molecules. Specifically, the last is employed to attract and concentrate different components from the cellular milieu.

Our lab is focused on understanding the self-organization of protein mixtures through the study of their interactions at the molecular level. In this sense, protein interactions can result in differently organized assemblages with diverse biophysical properties and biological purposes. They can build strong and resistant amyloid fibrils with structural, adaptative and epigenetic purposes. But also, active, sensitive and modulable biological condensates with metabolic and regulatory functions.

STRATEGIC OBJECTIVES

- Microbiota and neurodegenerative diseases
- Proteins and RNAs in membrane-less organelles
- Fitness costs and benefits of protein aggregation
- Biophysical characterization of protein aggregation

MAIN RESEARCH LINES

Microbiota and Neurodegenerative Diseases

We aim to shed light on the relationship between the intestinal microbiota and the development of neurodegenerative diseases. Computationally we will look for possible prions among the proteins encoded in the gut microbiota. Then in a test tube, we check that the selected candidates are able to aggregate and that they can transmit this aggregation to human proteins. Finally, we analyse in living and neuronal cell models whether these prions can generate neurodegenerative phenotype. This can influence our understanding of neurodegenerative diseases and can inspire alternative therapies for their prevention and treatment.

Proteins and RNAs in membrane-less organelles:

Proteins and RNAs assemble in membrane-less organelles that organize intracellular spaces and regulate biochemical reactions. The ability of proteins and RNAs to form condensates is encoded in their sequences, yet it is unknown which domains drive the phase separation (PS) process and what are their specific roles. Here, we systematically investigated the human and yeast proteomes to find regions promoting condensation. Using advanced computational methods to predict the PS propensity of proteins, we designed a set of experiments to investigate the contributions of Prion-Like Domains (PrLDs) and RNA-binding domains (RBDs). We found that one PrLD is sufficient to drive PS, whereas multiple RBDs are needed to modulate the dynamics of the assemblies. In the case of stress granule protein Pub1 we show that the PrLD promotes sequestration of protein partners and the RBD confers liquid-like behaviour to the condensate. Our work sheds light on the fine interplay between RBDs and PrLD to regulate formation of membrane-less organelles, opening up the avenue for their manipulation

Fitness costs and benefits of aggregation

Phase separation of soluble proteins into insoluble deposits is associated with numerous diseases. However, protein deposits can also function as membrane-less compartments for many cellular processes. Consequently, there is controversy about the fitness costs and benefits of forming such deposits. In this work, we combined a protein model that phase-separates into deposits and a mathematical equation, to distinguish, isolate and quantify the fitness contribution due to (i) the loss or (ii) gain of protein function and (iii) deposit formation. We used this approach to measure these contributions in different conditions. We observed that the environmental condition and the cellular demand for the protein function were key determinants of fitness. In addition, we showed that protein deposit formation can influence cell-to-cell variation in free protein abundance between individuals of a cell population (i.e., gene expression noise). Overall, this property results in variable manifestation of protein function and a continuous range of phenotypes in a cell population, favouring survival of some individuals in certain environments. Thus, this data suggests that protein deposit formation by phase separation might be a mechanism to sense protein concentration in cells and to generate phenotypic variability. Moreover, we have demonstrated that the selectable phenotypic variability, previously described for prions, could be a general property of proteins that can form phase-separated assemblies and may influence cell fitness.

https://sites.google.com/view/degrootlab/página-principal

LAB FEATURED PUBLICATIONS

(* corresponding author)

Seira Curto J., Surroca Lopez A., Casals Sanchez M., Tic I., Fernandez Gallegos M.R., **de Groot N.S.*** Microbiome Impact on Amyloidogenesis. Frontiers in Molecular Bioscience 9:926702. (2022)

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Armaos A., Zacco E., **de Groot N.S.*,** Tartaglia G.G. RNA-protein interactions: Central players in coordination of regulatory networks BioEssays 43(2):e2000118 (2021)

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de Groot, NS; Torrent Burgas, M. A coordinated response at the transcriptome and interactome level is required to ensure uropathogenic escherichia coli survival during bacteremia. *Microorganisms. 7(9). pii: E292. 2019*

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Pallares, I; **de Groot, NS**; Iglesias, V; Santana, R; Ventura, S. Discovering Putative Prion-Like Proteins in Plasmodium falciparum: A Computational and Experimental Analysis. *In Frontiers in Microbiology. 9:1737. 2018.*

Batlle, C; **de Groot, NS**; Iglesias, V; Ventura, S. Characterization of Soft Amyloid Cores in Human Prion-Like Proteins. Scientific Reports. *7, 12134. 2017.*

Chavali, S; Chavali, P; Chalancon, G; **de Groot, NS**; Gemayel, R; Latysheva, N; Ing-Simmons, E; Verstrepen, KJ; Balaji, S; Babu, MM. Constraints and consequences of the emergence of amino acid repeats in eukaryotic proteins. *Nature Structural and Molecular Biology. 9, 765-777. 2017.*

Carijaa, A; Navarro, S; **de Groot, NS**; Ventura, S. Protein aggregation into insoluble deposits protects from oxidative stress. *Redox Biology. 12, 699-711. 2017.*

Crua, N; Muñoz, E; de **Groot, NS***; Torrent, M. Centrality in the host-pathogen interactome is associated with pathogen fitness during infection. *Nature Communications. 8, pp. 14092. 2017.*