Histones – a group of proteins that facilitate packaging of DNA molecules – have been known about since the 19th century, but it is only recently that their true importance has been discovered. The Chromatinmolevol project seeks to examine histone variants and their role in chromatin dynamics

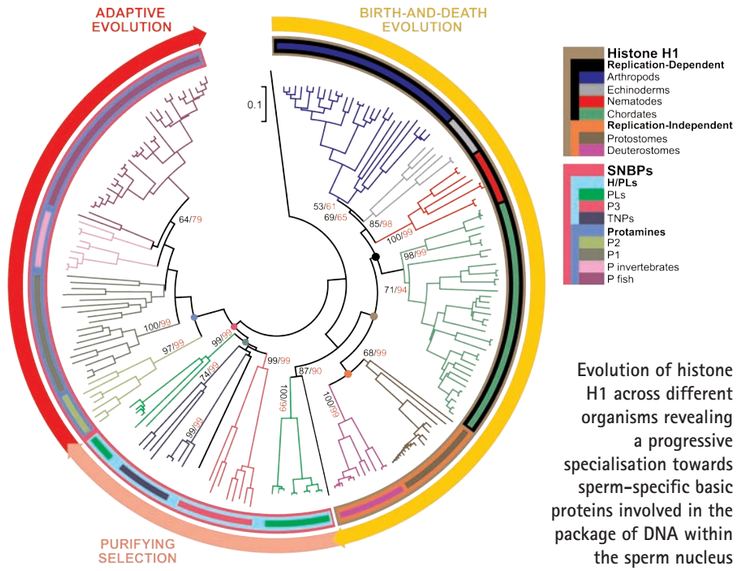
Unlocking tangled secrets of the DNA molecule

Nowadays we all are aware that in living organisms (except for the case of some RNA viruses) the genetic information is contained in the DNA, a key molecule present in each one of the cells constituting an organism. Given that the DNA molecule is more than a metre in length, it is astonishing how it is able to fit not only within a single cell but within the cell nucleus, an even more reduced space. Such an extreme packaging is mediated by a group of proteins known as histones, which interact with DNA configuring the chromatin fibre.

Although histones were considered as merely structural elements since their discovery in the 19th century, studies carried out almost a century later (late 1980s) revealed that they are also key players in regulating dynamic processes inherent to chromatin metabolism such as DNA replication, transcription and repair. Such discovery traced a direct link between histones and genetic alterations leading to pathological states such as cancer and other diseases, representing a rebirth in chromatin and histone research.

The Marie Curie project acronym CHROMATINMOLEVOL simply stands for the "Molecular and evolutionary characterisation of core and linker histone variants: mechanisms involved in altered chromatin conformations arising from pathological states", and is focused towards the structural and evolutionary characterisation of different histone types and their role in chromatin dynamics, with special emphasis on altered DNA conformations arising from pathological states.

This project is funded by the European Commission through an Outgoing International Fellowship within the Marie Curie Individual Actions Programme of Human Resources and Mobility (Project MCA-OIF 021900), and has been developed by Dr. José M. Eirín-López (researcher recipient of the fellowship) in collaboration with Professor Juan Ausió at the outgoing institution (Department of Biochemistry and Microbiology, University of Victoria, Canada) and with Professor Josefina Méndez at the returning institution in the European Union (Department of Cellular and Molecular Biology, University of A Coruña, Spain).

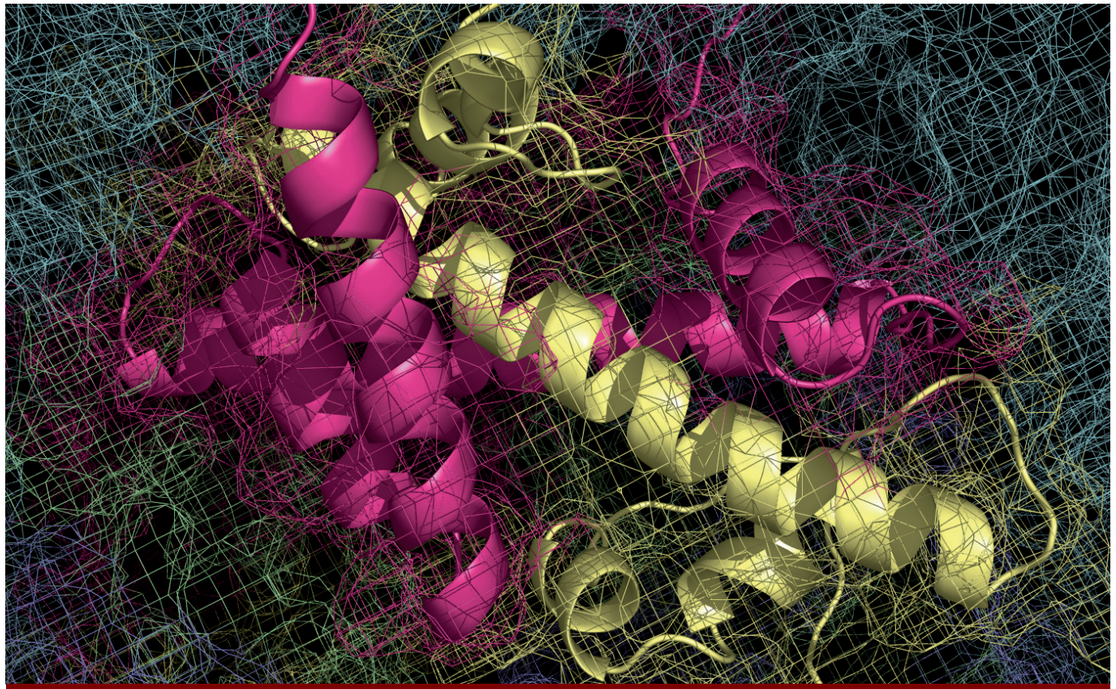


Evolution of histone H1 across different organisms revealing a progressive specialisation towards sperm-specific basic proteins involved in the package of DNA within the sperm nucleus

Major achievements

The CHROMATINMOLEVOL project is divided into three main objectives, including the characterisation of new histone variants, the study of the evolutionary mechanisms leading to their functional diversity and the characterisation of histone-DNA complexes. Three major achievements stand out in this project due to its innovative nature and the contribution they make to the state-of-the-art in the chromatin field.

First, the role of two critical histone variants (H2A.Z and H2A.Bbd) has been deciphered; second, the molecular evolutionary mechanisms leading to the functional specialisation of different histones have been determined; and third, the study of DNA and its associated proteins in spermatozoa has allowed to trace how histones and other sperm proteins affect



Representation of the 'handshake' interaction between histones H2A (yellow) and H2B (red) configuring a histone dimer critical for the packaging of DNA in the cell nucleus

fertility and sperm competition in humans and other mammals.

To date, this project has resulted in the publication of 14 international peer reviewed research papers and in seven scientific communications to international congresses in the molecular biology and chromatin fields. Furthermore, this work has complemented the objectives of three other research projects funded by public bodies from Canada and Spain, leading to international collaborations with European and American research institutions.

Such results make this project outstanding in terms of research production and achievement of the proposed objectives, together with the concomitant reinforcement of the international dimension of the career of the fellow and the increase in the research excellence of the European Union

There follows, by Dr. José M. Eirín-López (researcher recipient of the fellowship), a description of the international approach to the role of researcher as facilitated by Marie Curie Actions.

It is important to choose world-recognised research centres as potential outgoing institutions in order to be successful, given that one of the most important objectives of the OIF fellowships is to train researchers

What is the role of the Outgoing International Fellowships within the Marie Curie Actions (OIF-MCA) and who are the potential applicants for this programme?

Through this individual fellowship, the European Commission aims to reinforce the international dimension of the career of European researchers by giving them the opportunity to be trained in a world level third country research organisation and then to apply the experience gained in a return host institution in a Member State or Associated State. Applicants are typically early stage postdoctoral researchers (no more than three years since the defence of their Ph.D. degree) with an outstanding research record, seeking a postdoctoral training in the best research centres in their field outside Europe.

How are outgoing and return institutions selected by the applicant?

Generally, the applicant contacts with consolidated researchers, both at the outgoing and the returning institutions, interested in developing a research project in a concrete field. It is important to choose world-recognised reference research centres as potential outgoing institutions in order to be successful, given that one of the most important objectives of the OIF fellowships is to train researchers only at top institutions outside Europe.

How does the MCA-OIF program promote the development of the research career from the applicant investigator?

The OIF program makes special emphasis in increasing the international dimension of the research career of successful applicants by funding their mobility to research centres

Professor Josefina Méndez , Professor Juan Ausió and Dr. José M. Eirín-López

overseas, responding to the researchers' needs in terms of complementing their training in inter/multi-disciplinary research, research management skills and intersectorial mobility.

What is the expected scientific contribution of MCA-OIF fellows to the outgoing and the return institutions and what are the expectations for a MCA-OIF fellow once the project has finished?
In the first phase, the researcher is expected to increase and expand the research potential of the outgoing institution, taking advantage of the expertise of such institution in the field. During the returning phase the researcher is expected to set up the conditions necessary in order to finish the project and to bring the research lines initiated overseas back to the European return institution. Once the fellowship ends the researcher has achieved a high degree of independence which, together with the international dimension of the research, makes feasible his/her integration within the return institution.

What are the circumstances which led you to your work?
When I started to work as a my Ph.D. work fellow in Dr. J. Méndez Laboratory at the University of A Coruña (Galicia, Spain) my main interest was focused on the genomic structure and evolution of the histone family in molluscs (Galicia is the world-leader in harvesting and exporting this organism for fresh food and canning industries). The turning point came when, at some point of my thesis, I decided to include chromosomal proteins from all animals and plants known to date in the analyses. By such genome-wide characterization of different histones I gained a strong background on chromosomal proteins and, most importantly, my work was accessible for a broader audience in the chromatin field allowing me to contact Dr. J. Ausió at the University of Victoria (Canada) and to start the present project.

How would you describe the significance of the work derived from this project for your field?
Alteration in expression of specific genes involved in growth regulation can result in malignant transformation. Our work has contributed to the increasing awareness of the role of chromatin structure and evolution in the regulation of gene expression and in the genesis or suppression of different pathologies. Understanding such mechanisms has resulted in the discovery of new therapeutic strategies used in the treatment of cancer.

Where do you see this research going 10 years from now?
Our attention will be on the role of such histone variants in determining concrete chromatin structures and the potential interactions with modifying enzymes in signal transduction pathways. The potential for DNA structure is still to come. What is most important is to see what it looks like in terms of other DNA binding proteins and regulatory factors, and how these structures differ from the structure in solution. How does it repair itself, for example? This question is at the base of many diseases, including cancer. In eukaryotic cells the right context is to look at it in chromatin, and that is where the impact of our structure comes: it is the structure of DNA in the context of the way it actually is in the cells. We cannot make progress by looking at interactions between naked DNA and proteins, because that is not the real world of the life of the cell. ★

At a glance

CHROMATINMOLEVOL
Molecular and evolutionary characterization of core and linker histone variants: mechanisms involved in altered chromatin conformations arising from pathological states

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Dr Jose M. Eirín-López has been active in the field of molecular evolutionary genetics since 1999, receiving his Ph. D. in Genetics from the University of A Coruña (Spain) in 2005. He joined the Laboratory of Dr. Juan Ausió at the University of Victoria (Canada) as a Marie Curie postdoctoral researcher in 2005 and since 2008 is a Researcher at the Department of Cellular and Molecular Biology at the University of A Coruña. He is a frequent peer reviewer for international publications and is currently participating in different national and international research grants.