

Epigenetic control of cell fate - an interview with Maria-Elena Torres-Padilla

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ABSTRACT Maria-Elena Torres-Padilla's research is focused on how cell fate arises from a single-cell embryo, the fertilized egg or zygote. After the initial divisions, cell potency becomes restricted, originating the first cell lineage fates. She studies how epigenetic information controls transitions in cell identity and cellular reprogramming during embryonic development. Currently, she is the founding Director of the Institute of Epigenetics and Stem Cells, Helmholtz Centre, and Professor of Stem Cell Biology at the Ludwigs Maximilians University in Munich. In this interview, Maria-Elena Torres-Padilla talks to us about her beginnings in the biology field in Mexico. She also tells us about how she became interested in the control of genome regulation within the nucleus during the transition from totipotency to pluripotency and how the control of gene regulation and chromatin organization during the early stages of cell fate decision in the one-cell embryo occurs. She considers that science has no borders; visiting Mexico gives her the possibility to discuss her work with colleagues and the new generation of students trained in Mexico.

KEY WORDS: *totipotency, pluripotency, early embryo, epigenetics, chromatin architecture*

Introduction

The embryonic development of metazoans begins with the fertilization of the egg. The one-cell embryo generates all the tissues of the whole embryo and the extra-embryonic structures. During the first cell divisions, the resulting cells progressively restrict their potential, becoming pluripotent, multipotent, or unipotent, upon the establishment of the fates of the first cell lineages (Fig. 1). Chromatin within the cell nucleus is organized in two forms, euchromatin and heterochromatin. In the former, chromatin is packed in a less tight manner and therefore is defined as accessible, "open" chromatin. Here, histone acetylation contributes to gene transcription. In contrast, heterochromatin is characterized as densely packaged or "closed." Heterochromatin is associated with specific histone methylation patterns, for example of H3K9me3, that are thought to promote silencing. The early embryo is thought to have a rather 'open' chromatin structure. Historically this more loosened chromatin layout has been thought to result from or to promote epigenetic reprogramming at the beginning of mammalian development (Jansz and Torres-Padilla, 2019, Iturbide and Torres-Padilla, 2017).

Prof. María-Elena Torres-Padilla was born in Mexico. She obtained a Degree in Biology at the Universidad Nacional Autónoma de México, at the Faculty of Sciences. She completed her Ph.D. with Mary Weiss at the Pasteur Institute in Paris, France, and her postdoctoral training with Magdalena Zernicka-Goetz at the Gurdon Institute in Cambridge, UK. She started her lab at the Institut de Génétique et de Biologie Moléculaire et Cellulaire (IGBMC) in Strasbourg, France in December 2008. Currently, she is the founder Director of the Institute of Epigenetics and Stem Cells, Helmholtz Centre, Munich, Germany and Professor for Stem Cell Biology at the Ludwigs Maximilians University in Munich, Germany. Throughout her career, her focus of research has been to understand the mechanisms governing cell identity, initially through understanding cell communication and signaling, the action of transcription factors, and for the last years, her focus has been chromatin regulation and epigenetics, in particular, how they regulate cellular plasticity and reprogramming.

Dr. María-Elena Torres-Padilla's research aims at understanding chromatin organization and chromatin states during the

Abbreviations used in this paper: UNAM Universidad Nacional Autónoma de México.

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Fig. 1. The mouse blastocyst after 3.5 days of development. DNA was stained with DAPI (red) and cell-cell membranes are highlighted in magenta, based on phalloidin staining for cortical actin. The two first lineages of the blastocyst, the inner cell mass and the trophectoderm, can be appreciated.

establishment of totipotency in the zygote and the subsequent first cell-fate decisions, using the mouse as an animal model. She and her laboratory seek to understand how the molecular mechanisms of epigenetics control the chromatin organization and regulate the establishment of totipotency, and how totipotency is lost. Furthermore, her view of epigenetic goes beyond looking at the regulation of chromatin by studying how acetylation regulates promoter activity. She is more interested in the phenomenological part, that is, in the understanding of how epigenetic reprogramming controls chromatin configuration during cell fate determination and cellular plasticity, how the phenotype emerges from the genotype to control cell identity (Torres-Padilla, 2020). Her laboratory is composed of members of different nationalities, as many laboratories in Europe, including students from Latin America. However, she does not make the selection of students based on nationality. Science has no borders! (Fig. 2). The scientific contributions (<https://pubmed.ncbi.nlm.nih.gov/?term=torres-padilla&sort=pubdate&size=200>) of Prof. Torres-Padilla have garnered her the praise of the scientific community. She received the German Stem Cell Network (GSCN) 2018 Female Scientist Award for her outstanding research on how early embryonic development is controlled by chromatin regulation, and how the establishment of totipotency in the zygote and the subsequent first cell-fate decisions in mouse embryos occurs. She is an elected EMBO member and was recognized for her outstanding leadership trajectory as Extraordinary Young Scientist by the World Economic Forum (<https://www.youtube.com/watch?v=xgHxXamtUWQ>) (Fig. 3). She is part of the editorial board of *Genes & Development*, the *Journal of Cell Biology and Development*, and has been recently made Honorary Skou Professor at the University of Aarhus, Aarhus, Denmark.

In the following paragraphs, we present the very candid interview held with Dr. Maria-Elena Torres-Padilla by videoconference in November of 2019. Here, she highlights her scientific career as an epigeneticist and developmental biologist.

Tell us a little about your academic training.

I studied biology at the Faculty of Sciences of the Universidad Nacional Autónoma de México (UNAM). After graduating, I went to the Pasteur Institute for my doctorate studies and obtained my degree from the University of Paris V. Then, I did a four-year postdoctoral training at the Gurdon Institute of the University of Cambridge, England. It was during this period that, for the first time, I became truly devoted to studying aspects related to developmental biology. After that, I spent two years with Lázlo Tora in Strasbourg, to learn more about biochemistry. The idea was to learn some biochemistry approaches and to apply molecular and mechanistic techniques to pre-implantation mouse embryos, of which not much had been done in the past. End of 2008, in December actually!, I started my group as an independent researcher in Strasbourg. In 2016, I moved to Munich, to continue pursuing the same lines of research, and found the Institute of Epigenetics and Stem Cells, of which I am currently the Director.

During your academic training in Mexico, you spent time at the laboratories of Dr. Librado Ortiz and Dr. Adolfo García-Sainz. What led you to enter their laboratories?

While studying biology, I was convinced that parasites were a wonderful thing, and I was extremely interested in learning more about them. Dr. Ortiz's laboratory was one of the leading laboratories studying amoebiasis. Because amoebiasis was a significant health problem in Mexico at that time I spent a year in his laboratory (Torres-Padilla *et al.*, 1997). I was curious about learning what a parasite does to our body, and the strategies of their survival, which are fantastic. It was partly because of that, that I thought about learning more about cell communication and signaling through receptors. The expert in those fields in Mexico was Dr. García-Sainz, who was recognized world-wide, so I spent my last three years of University at his laboratory in the Institute for Cellular Physiology at UNAM. I used to take my courses during the mornings and spent the afternoons in the laboratory. I believe this was essential to engage in research and experimentation quickly, learning how to make a scientific reflection and how to design a good experiment (García-Sainz and Torres-Padilla, 1999; Medina *et al.*, 1998). It is very fortunate that in Mexico we have the opportunity to enter a laboratory early in our careers. I am convinced that it is very important for training and for developing scientific curiosity, and I had landed in a top place!

What drove you to follow a scientific career?

I think at least two reasons. The 'earliest' and probably very decisive, was my biology teacher in high school, who was terrific! She knew how to awaken my curiosity about asking myself how life works, questions I had since I was a child I wanted to understand what I saw happening around me, especially on a molecular level. I always wanted to understand how life works. I had some doubts about whether to study medicine or biology, but since I knew I wanted to do research from an early age, I decided for biology. I wanted to maintain a broad view of life sciences and not only dedicate myself to the human being but also to look at all the animal kingdom, protozoa, paleontology and so on. At that time, the programme of the Biology degree at the Faculty of Sciences was extensive and fabulous. There I learned about ecology and geology, from the smallest mollusk to plants, passing of course through virus and evolution. It was



Fig. 2 (Left). Maria Elena during the 2018 Abcam meeting.



Fig. 3 (Right). Maria Elena Torres-Padilla. Source: WEF. As co-chair of the AMNC meeting of the World Economic Forum in 2017. "Being asked to co-chair the AMNC was a huge honour and something I was very glad to accept" said ME Torres-Padilla "it gave me the perfect opportunity to raise awareness for the need for future funding of basic research and for the need for scientists to engage with the public, something I believe to be integral to securing scientific and technological advances in the future"

a complete program, and that was what I was looking for. I felt very rewarded by studying all these!

You said your high school biology teacher was a determining factor. Who was your teacher?!

I studied at the Miguel Angel Institute in Mexico City which was a high school where my mother, grandmother, and aunts studied – so very conservative – and a long tradition in my family! My teacher was a biologist from the Universidad Autónoma Metropolitana in Mexico City. Julieta was her first name, and I still remember her books, even more, her perfect classes. She once explained to us the conjugation process of the *Paramecium*. I was astonished, and I still remember that class, more than 20 years later.

Since you were a graduate student, you became interested in the regulation of gene expression by extracellular signals. Specifically, how did your interest in developmental biology come about?

For my doctorate, I worked with orphan receptors (Bailly *et al.*, 2001; Torres-Padilla *et al.*, 2001; Torres-Padilla *et al.*, 2002; Torres-Padilla and Weiss, 2003). Since there was no signaling pathway associated with a known ligand for them, I turned my attention to gene regulation mediated by this type of receptors. By the end of my Ph.D., I was studying how these receptors interacted with or modified chromatin. One of the last experiments I did was to see if the receptors I was working with, interacted with HDACs (histone deacetylases) differently, and found that indeed that was the case (Torres-Padilla *et al.*, 2002). When starting to decide what I would do for my post-doctorate, I considered two options. I knew what I wanted to study, I wanted to study chromatin regulation in a biological relevant system. One option was choosing a laboratory that studied chromatin because I thought

it was a way to comprehensively understand the changes in gene regulation, not only of a particular gene or receptor but also of the genome and epigenome with a broader standpoint. A second option was to gain expertise in a model system where I could apply those approaches in a specific context. It seemed to me, perhaps in a naïve way, a bit easier to export molecular biology and biochemistry protocols, such as Western blotting or Chromatin immunoprecipitation to another system, rather than trying to learn a new model on my own, embedded in a molecular biology laboratory. In the end, I decided to go for the model system. I realized that very little was known in terms of global gene regulation in the early mouse pre-implantation embryo, so I thought it would be very cool to study. My idea was to find a system in which I could study how chromatin regulates the output of cell fate decisions; that is, why a cell differentiates in one direction and not the other. In that sense, the decisions made during pre-implantation mouse embryo development represented the perfect model (Fig. 4). With that in mind, I applied for a postdoc position in the lab of Magdalena Zernicka-Goetz at the Gurdon Institute in Cambridge, UK, and I think there is where my focus on developmental biology really began.

Why the mouse and not another model?

In part, because I was already used to working with that animal model, I did my Ph.D. working primarily with mouse cells and even with some tissues extracted from mice. Also, because many molecular and genetic approaches were in theory more easily applicable. But more than anything, because of the variety and importance of the questions to address cell fate decision in pre-implantation embryos. Really, without dismissing any model system, where can you find an organism in which you can easily observe obvious phenotypes in terms of implantation or pluripotency, which also goes through different cell divisions before

reaching those stages? I also had interest and curiosity about other organisms, but not enough to work with them. Honestly, I was not pursuing developmental biology, *per se*. I was looking for a system where I could see changes in cell fate and that I would study gene regulation. It was not the development question *per se*, but the reprogramming question of epigenetics that led me to the system in that regard. I still remember years later, at a meeting, someone told me that I was a developmental biologist, and I was sort of ‘self-shocked’ – I never viewed myself as such – but obviously I WAS doing developmental biology. To put it short, I just think it was the right model system for the questions that I wanted to address.

In this sense and starting clearly from the knowledge that you have now and that way of seeing things, if you were to go back in time, would you think of focusing on a developmental biology question?

I do not know if you are asking me what I am doing right now. I guess my answer would be, if the question is related to plasticity, and cell identity, in that sense, yes. It seems fantastic to me that a single cell, the zygote, can form a whole organism. I find it extraordinary that the genetic material, the chromatin, and their unfolding, allow that. In that sense, I would say yes, because finally, the only system where you can study that, by definition, falls into the developmental biology field. The truth is and it was more or less the reason I do not consider myself a ‘mainstream’ developmental biologist, is that for many years, the biochemical and molecular approaches in developmental biology questions were not really sought after. The field was and has been primarily driven by genetics. And at that time, genetics was so powerful that every meeting I attended, people would present a knock-out and a phenotype. And that was it. Coming from a very quantitative pharmacological training with García-Sainz, I felt incomplete. Really, what interests me is understanding what happens to the cell. OK, there is a phenotype, but why? I felt that the focus of developmental biology, 10 or 15 years ago, was a little bit that. In response to that question, my passion is to understand the

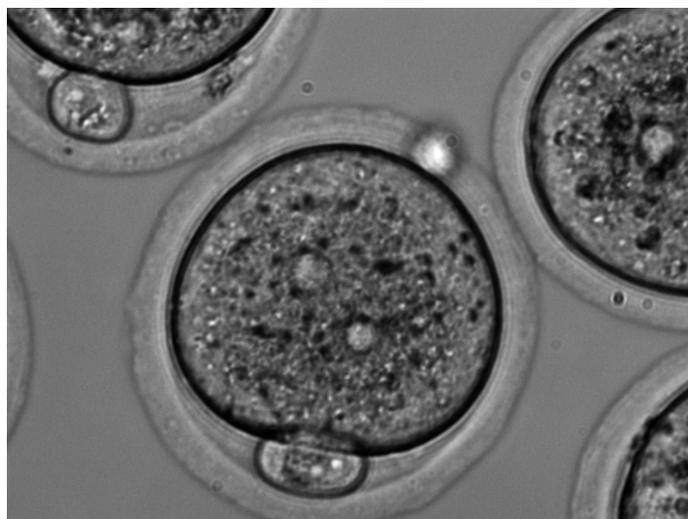


Fig. 4. A mouse zygote a few hours after fertilization imaged under brightfield optics. *The maternal and paternal pronuclei can be distinguished in the center, by the presence of visible round nucleolar-like bodies (nucleoli precursors).*

zygote’s ability to do everything based on how the chromatin orchestrates the transcriptional and signaling programs, which eventually interplay with the metabolic and environmental cues (Burton & Torres-Padilla, 2014). So, I think in the end, the answer is yes and no.

If I had to decide again, it is evident that I would not work with just HeLa cells, for example (no offense!). The biological context for me is critical, an epigenetic phenotype is what I would choose in the end, because the question we are trying to answer comes down to epigenetics. I do not strictly feel I am a developmental biologist. I certainly will not study gastrulation, for example; it has much more complex and essential developmental issues. I had never thought about this before, but now that you ask me, what interests me is the epigenetic phenomenon. And since the embryonic development, by definition, is epigenetic, then in that sense, well, yes, I am studying embryonic development (Fig. 5).

What do you value most from what you learnt during your postdoc at the Gurdon Institute in Cambridge?

What I learned in my postdoc, in the lab of M. Zernicka-Goetz was to manipulate and embrace the model system. There I gained expertise in working and manipulating early mouse embryos. That was exactly what I was looking for, and I wanted to work in a laboratory that was a pioneer in modern experimental embryology. The most important thing for me was to broaden my view, learn as much as possible to perform embryological manipulations that I could do with the mouse embryo, but my goal was to bring molecular biology to the early developing mouse embryo, to use the mouse embryo to study cell and molecular biology. In that sense, the environment at the Gurdon Institute was key, I learnt so much, and was lucky to meet many people, fully committed and outstanding postdocs in every lab of the Institute.

Regarding my scientific education, I think Dr. García-Sainz was the one that had one of the most significant impact, if not the most one, in terms of rigor, demand, and structure. The time I spent with him was fundamental for my training and the way I do science now. He is one of the most efficient, careful and sharp scientists I had the chance to work with. In the laboratory where I did my Ph.D. with Dr. Mary Weiss, I learned the structure of cell biology, that I did not have previously. In Mexico, what I learned was signal transduction and receptor pharmacology. These both angles have been very helpful. Younger generations should see that following a straight line is not necessarily good, but seeing different approaches from different laboratories -and disparate topics- is very enriching.

How do you define epigenetics, and how do you associate your concept with the one proposed by “Waddington”?

I am a bit old fashioned. I believe that modern epigenetics, as we now understand it in our role as developmental biologists or epigeneticists, is based on what Waddington proposed (Waddington, 1957). In the field of epigenetics, there is a definition that is mainly molecular and not phenomenological. I think I am more in the phenomenological one, although obviously, what I am interested in is bringing the molecular part of epigenetics to phenomenology. I think my laboratory really is a bridge between the two. I believe that chromatin biology alone, for instance, by studying histone acetylation of a particular promoter, is not

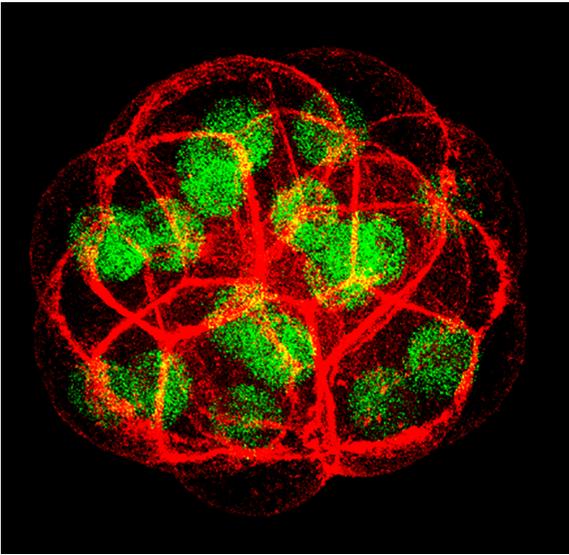


Fig. 5. The mouse embryo at the 16-cell stage, stained with an antibody for methylated histone H3 (green) and for cortical actin (red) to depict cell-cell boundaries, reconstructed in 3D after confocal microscopy.

epigenetics; that is, regulation of transcription through chromatin-related mechanisms, which can potentially be part of epigenetics, but it is not epigenetics *per se*.

Can the study of cell differentiation be explained only by epigenetic regulation?

That is an interesting point, which can be seen from different perspectives. In my view, it is the regulation of the chromatin structure that enables the acquisition of a cellular identity. Now, regarding the microenvironment, the signaling, obviously they are essential. But some people say that what is most important is a triggering signaling pathway. For me, everything starts from the nucleus, but on the other hand, if you do not have the signaling, it cannot work.

Once, when I spoke at a conference about an ectopic expression of chromatin modifiers in one of the cells of the embryo, for which the cell fate of the progeny changed, we had concluded that modifying chromatin is enough to change the cell fate. However, a colleague jumped out of her chair and said, “you cannot say that only transcription factors can change fate.” This was an interesting reaction, which I often encounter nowadays when I discuss with colleagues. But in the end, I argue, thinking just about transcription factors is straightforward for the human being to understand. That is because we know the code, and we can recognize a specific regulatory sequence in the DNA, and can easily picture that the transcription factor will go bind its cognate binding site and activate (or repress) transcription. But the chromatin can be instructive too. The fact that we do not yet understand how chromatin modifiers can mediate specific gene regulatory outputs – in other words, how chromatin modifiers are targeted to specific genomic sites – does not mean that the chromatin does not act as a cell fate determinant. Chromatin *per se* is not going to do anything; obviously, it needs transcription to be present and trigger this, but if the chromatin does not promote (or respond), nothing happens either. I do believe that epigenetics is a determinant of cellular identity.

It is evident that epigenetics and cellular fate is what interests you, but how else could you study the same phenomenon?

It seems to me that biophysics is a discipline that has directly contributed a great deal, especially over the last ten years, to cell identity. Examples of this are single-molecule tracking or understanding how “mechano-transduction” affects cellular identity. I think those are immensely powerful experimental approaches. In the end, I think that it also impacts chromatin. A very recent study from the lab of Sara Wickström, for example, is a beautiful demonstration of this (Nava *et al.*, 2020).

How do you deal with the academic-administrative part? What impact does it have on the work of your laboratory?

It has some impact, I guess, but I trust the impact is good. This is a question that you probably better ask the people in my lab! My role as Director can also impact back, some benefits to the lab, mainly because having this type of commitment allows me to have an impact on other issues such as science policy and priorities. You get to know different kinds of people. As we become older, also some things are done more efficiently. What used to take me a week to do now takes me half a day, which opens up some time for other commitments. What I do most of the time is talk to people and discuss projects, and this is my most rewarding activity. I trust that my position as Director, even though it takes time, it has many advantages for the people I work with in the laboratory and for me. In the end, the lab has a much broader exposure than if we were alone.

All epigenetic regulation processes are related to cellular reprogramming phenomena. In that sense, are you particularly interested in regenerative medicine, is your Center somehow involved in this area?

That is done a lot in the Center. My Institute is part of a much larger Center formed by several institutes, the “Stem Cell Center”. One of our objectives is to contribute scientifically and with more translational approaches to what we know as “cell replacement therapy”. Some of my colleagues have done very exciting work towards this direction, and that also offers possibilities for our work, to project our findings to different avenues. Our projects themselves are more focused on basic research, but with the interactions I have with colleagues, which are fascinating, I can see the scope of research from different perspectives. For instance, the “pathways” we have described as relevant for reprogramming a cell towards totipotency features, are also required for the reprogramming of induced pluripotent stem cells (Ishiiuchi *et al.*, 2015, Torres-Padilla, 2020). Therefore, I believe that revealing the basic molecular mechanisms can have a positive influence in the field; consequently, it is a priority of our Center.

Having this position as Director, do you consider important the communication of the generation of knowledge to the public and to the people who make decisions? Do you think that Developmental Biology has a significant impact on society? What influence do you have?

Of course, I think it should. I feel disappointed that scientists have lost respect from society, in some parts of this planet more than in others. I believe we have a responsibility to raise public awareness to generate interest and understanding of the phe-

nomena and processes that we investigate. I feel I have not done enough because it will never be enough, but I am interested in communicating with the public and discussing ethical problems. Even discussing issues related to conflict of interest in decisions or scientific fraud. One must speak in an informed way, not simplifying as if the public were ignorant; that is the worst thing one can do. People are knowledgeable, and we must generate an interest in what we study and communicate what the limitations and the potential are. I think there is a lot of confusion in the public, for example, about stem cells. For instance, at a conference that I was at a while ago, someone thought that every time an experiment was done with human stem cells, an embryo got killed. That is not true, but that kind of confusion is what makes the public say that it is not ethically right to work with human stem cells. We could talk for hours on this theme, but that is not the purpose of the interview. However, I believe that the public understands the research process, and the implications that it may have, whether good or bad, are key (Fig. 3).

Have you trained students from Latin American?

Yes, I have. One of them, for example, is Mexican, Diego, he received his doctoral degree in April 2019, and he did outstandingly well. But I do not make the selection of my students based on nationality, I think that would be very bad. I try to go to Mexico when I can, and fortunately, they still invite me to speak at conferences. It is an excellent excuse for me to return to Mexico and talk for a while with the people. Visiting Mexico is an excellent opportunity to discuss our work with my former colleagues, and with the new generation of students trained in Mexico, and motivate their curiosity for science. Also to show, and hopefully, to inspire them, that science has no borders. That the training that I received, liked them, at the UNAM, was extremely important for my career as a scientist in an international scenario. I was at the UNAM main campus in November last year, and I was invited to go to the Institute of Genomic Sciences in UNAM this year. They kindly asked me to give a talk as a part of the Frontiers in Genomics program (but the coronavirus!). I am always very happy because they are interested in our work and that is very satisfying.

What do you think has been your contribution to knowledge in the field?

That is a complicated question to answer. I sometimes think that there is still so much work to do. Every person in my lab, every project takes a lot of effort. And sometimes in the end when we try to put things in the larger perspective, I feel we advance very slowly. As we say in Mexico, taking tiny steps trying to understand a process that is so complex and so great. You ask me a complicated question, and I do not know if my colleagues working on the field will agree, but I think one of our contributions is trying to revisit molecular embryology, bringing molecular approaches to understand chromatin and its regulation in early embryos. When I started in my laboratory, there was hardly anyone doing that, and nowadays, the field is becoming very rich, trying to understand the question and find answers with very focused and sophisticated methods. We try to learn more about the mechanisms. For example, what we published three years ago regarding the role of retrotransposons in chromatin accessibility during pre-implantation embryo development was very new (Jachowicz *et al.*, 2017). This was a very crazy project when we started it, and I was lucky that Joanna,

in my lab was ready – and persevered! – to tackle that project. Maybe I should not say it, because it was our work, but it was the first work that tackled the question directly, are retrotransposons performing any function in embryos or not? We also published a paper this year on nuclear organization, the work of another Ph.D. student (Borsos *et al.*, 2019). There, for example, the technique itself was not so new, because Jop Kind, the person we collaborated with, had done a fantastic work in optimizing this in cells in culture during his postdoc. But what we learnt by applying it to embryos was very interesting. The oocyte does not seem to pass over its nuclear organization with regards to the association to the nuclear lamina. Instead, it seems that a new organization arises *de-novo* in the fertilized egg.

What recommendations would you make to young people to choose a career?

To invest not 100% but 300% of their effort in what they like. My father used to tell me that mathematically this is not possible. The point is that dedication is essential, but you also have to have fun, like it, and have the enthusiasm. If not, it is not worth it.

If you could, which author of the classics would you like to have a conversation with and on what topic?

I would love to chat with Waddington. Or maybe even with Lamarck, perhaps more than Darwin. Lamarck had it all there, but he went in the wrong direction. That may sound a bit at odds, since Darwin is most recognized, but I would love to discuss his thoughts with Lamarck. Now THAT would be interesting!

References

- BAILLY, A., TORRES-PADILLA, M.E., TINEL, A.P., WEISS, M.C. (2001). An enhancer element 6 kb upstream of the mouse HNF4alpha1 promoter is activated by glucocorticoids and liver-enriched transcription factors. *Nucleic Acids Res* 29: 3495-3505.
- BORSOS, M., PERRICONE, S.M., SCHAUER, T., PONTABRY, J., DE LUCA, K.L., DE VRIES, S.S., RUIZ-MORALES, E.R., TORRES-PADILLA, M.E., KIND, J. (2019). Genome-lamina interactions are established de novo in the early mouse embryo. *Nature*. 569: 729-733.
- BURTON, A., TORRES-PADILLA, M.E. 2014. Chromatin Dynamics in the Regulation of Cell Fate Allocation During Early Embryogenesis. *Nat Rev Mol Cell Biol*. 15: 723-734.
- GARCIA-SAINZ, J.A., TORRES-PADILLA, M.E. (1999). Modulation of basal intracellular calcium by inverse agonists and phorbol myristate acetate in rat-1 fibroblasts stably expressing alpha1d-adrenoceptors. *FEBS Lett* 443: 277-281.
- ISHIUCHI, T., TORRES-PADILLA, M.E. (2014). LINEing germ and embryonic stem cells' silencing of retrotransposons. *Genes Dev* 28: 1381-1383.
- ISHIUCHI, T., ENRIQUEZ-GASCA, R., MIZUTANI, E., BOŠKOVIĆ, A., ZIEGLER-BIRLING, C., RODRIGUEZ-TERRONES, D., WAKAYAMA, T., VAQUERIZAS, J.M., TORRES-PADILLA, M.E. (2015). Early Embryonic-Like Cells Are Induced by Downregulating Replication-Dependent Chromatin Assembly. *Nat Struct Mol Biol*. 22: 662-71.
- ITURBIDE, A., TORRES-PADILLA, M.E. (2017). Starting embryonic transcription for the first time. *Nat Genet* 49: 820-821.
- JACHOWICZ, J.W., BING, X., PONTABRY, J., BOŠKOVIĆ, A., RANDO, O.J., TORRES-PADILLA, M.E. (2017). LINE-1 activation after fertilization regulates global chromatin accessibility in the early mouse embryo. *Nat Genet*. 49: 1502-1510.
- JANSZ, N., TORRES-PADILLA, M.E. (2019). Genome activation and architecture in the early mammalian embryo. *Curr Opin Genet Dev* 55: 52-58.
- MEDINA, L.C., VAZQUEZ-PRADO, J., TORRES-PADILLA, M.E., MENDOZA-MENDOZA, A., CRUZ MUNOZ, M.E., GARCIA-SAINZ, J.A. 1998. Crosstalk: phosphorylation of alpha1b-adrenoceptors induced through activation of bradykinin B2 receptors. *FEBS Lett* 422: 141-145.

- NAVA, M.M., MIROSHNIKOVA, Y.A., BIGGS, L.A., WHITEFIELD, D.B., METGE, F., BOUCAS, J., VIHINEN, H., JOKITALO, E., LI, X. GARCÍA ARCOS, J.M., HOFFMANN, B., MERKEL, B., NIESSEN, C.M., DAHL, K.N., WICKSTRÖM, S.A. (2020). Heterochromatin-Driven Nuclear Softening Protects the Genome Against Mechanical Stress-Induced Damage. *Cell* 181: 800-817.
- RODRIGUEZ-TERRONES, D., GAUME, X., ISHIUCHI, T., WEISS, A., KOPP, A., KRUSE, K., PENNING, A., VAQUERIZAS, J.M., BRINO, L., TORRES-PADILLA, M.E. (2018). A molecular roadmap for the emergence of early-embryonic-like cells in culture. *Nat Genet* 50: 106-119.
- TORRES-PADILLA, M.E. (2020). On transposons and totipotency. *Philos Trans R Soc Lond B Biol Sci* 375: 20190339.
- TORRES-PADILLA, M.E., CARRERO, J.C., ORTIZ-ORTIZ, L. (1997). A 148-kDa secretory proteinase from *Entamoeba histolytica*. *Arch Med Res* 28: 186-187.
- TORRES-PADILLA, M.E., FOUGERE-DESCHATRETTE, C., WEISS, M.C. (2001). Expression of HNF4alpha isoforms in mouse liver development is regulated by sequential promoter usage and constitutive 3' end splicing. *Mech Dev* 109: 183-193.
- TORRES-PADILLA, M.E., SLADEK, F.M., WEISS, M.C. (2002). Developmentally regulated N-terminal variants of the nuclear receptor hepatocyte nuclear factor 4alpha mediate multiple interactions through coactivator and corepressor-histone deacetylase complexes. *J Biol Chem* 277: 44677-44687.
- TORRES-PADILLA, M.E., WEISS, M.C. (2003). Effects of interactions of hepatocyte nuclear factor 4alpha isoforms with coactivators and corepressors are promoter-specific. *FEBS Lett* 539: 19-23.
- WADDINGTON, C. H. (1957). *The Strategy of the Genes*. Geo Allen & Unwin, London.

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