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INTERVIEW

An interview with Edith Heard

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A geneticist by training, Edith Heard's research interests centre on the epigenetic events underlying X chromosome inactivation during mammalian development. In January 2019, Edith takes over as the Director General of the European Molecular Biology Laboratory (EMBL), with responsibility for six research sites across Europe. Before her move to EMBL, she was the Director of the Genetics and Developmental Biology Unit at the Institut Curie in Paris, and she continues to hold a chair in epigenetics and cellular memory at the Collège de France. We met with Edith to discuss her research interests, her future plans for EMBL and the extent to which she considers herself a role model for women in science.

Let's start at the beginning: what got you interested in biology at the first place?

You might not believe it, but I never actually took a biology class in my whole life until I went to Cambridge, planning to study physics and astronomy. My first year was a disaster: I got a third. But I had to take some biology classes that year (as part of the Natural Sciences course) – I'd never seen a cell before, I didn't know what a nucleus or a mitochondrion was, and had a real 'wow' moment! I thought it would just be a side-line, and then I'd get back to my physics. But this is what's so great about the Natural Sciences course – one can really explore different topics in the first and second years. Biology seemed fascinating and exciting, though I felt totally lost, because I'd never done any before. Then in my second year, instead of physics, I took the biochemistry, pharmacology and 'animals' biology options. It literally felt almost as though I woke up at the age of 18 or 19, so that was really the beginning. I wasn't convinced I was going to do a PhD and I thought I'd probably do a Master's or maybe look at medicine. But in my third year when I took genetics, my teachers, including John Fincham (Head of Genetics at the time), convinced me that 'you've got to do a PhD'. And so I did.

You went to Mike Fried's lab at the Imperial Cancer Research Fund (ICRF) in London, to work on gene amplification in cancers. What drew you to that lab and that topic?

As I said, I was thinking about doing medicine, so I thought that if I was going to do biology I could do something medically relevant. In the genetics department library, they had abstract books from the Cold Spring Harbor Laboratory (CSHL) tumour virus meeting, and for some reason I started reading these and got hooked. So I applied to two institutes for a PhD, the ICRF and the Institute of Cancer Research and I received an offer from Mike Fried at the ICRF. My project was to use rat cells that had become transformed by gene amplification of a Polyoma virus oncogene and so I plunged into the complex and, in those days, murky world of cancer genomic analysis. After four years of cloning very large fragments of amplified DNA to try and understand how gene amplification arises thanks to its genomic sequence, I decided to move to what seemed like a less complicated field for my postdoc, developmental biology, where at least the genome doesn't change!

You moved to Paris for your postdoc, to work with Phil Avner on X chromosome inactivation (XCI) – a problem you've worked on ever since. How did you get into the field, and what did you start out doing?

I got interested in epigenetics during my PhD – before it became fashionable. I was using methylation-sensitive rare cutter enzymes to do long-range mapping, so I started to read up on DNA methylation and became very interested in it. Actually it was Peter Goodfellow who said to me that if I was interested in DNA methylation I should go and do a postdoc on XCI, and suggested Hunt Willard and Phil Avner. By that time, I'd met my partner, who is French, so I decided to join Phil's lab at the Pasteur Institute in Paris. His lab was interested in how X inactivation is initiated by the X-inactivation centre (Xic). The *Xist* gene was discovered in his lab and others just as I arrived there.

I started out from a genetics perspective, trying to map the Xic functionally using large chunks of DNA carrying Xist. I was using yeast artificial chromosomes to create transgenic mice and embryonic stem cells, but I couldn't isolate a functional element, that could trigger XCI when present as a single copy transgene, even on the largest fragments of DNA. So I started wondering about what

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might be missing in this system, which got me thinking about chromatin and nuclear organisation. I was convinced that nuclear organisation must be involved, but Phil wasn't so interested in this area at the time. Christine Petit (who was also at the Pasteur) said to me 'you have an idea – go and do a sabbatical somewhere abroad where you can explore it, and then come back and set up your own group'. So that's what I did. I had a CNRS (Centre national de la recherche scientifique) position which allowed me to go to CSHL for a sabbatical, as a visiting scientist in David Spector's lab. It was that year at CSHL that really took me from genetics to epigenetics. I set up cell biology techniques that allowed me to combine the detection of gene transcription, chromatin and nuclear localisation – and to look at the X chromosome's status during ES cell differentiation as XCI initiates.

While I was at CSHL I met Dave Allis, who came to give a talk. He had a bunch of antibodies in his pocket that could recognise specific histone modifications – this was in 2000, when such modifications were just being identified. I asked if I could try them and did the experiment that same day. The next morning, I looked at the experiment I'd set up the night before, and I could see that the X was rich for K9 methylation, and excluded for K4 methylation. I sent Dave Allis the pictures; he was so excited about what we were seeing; within 1 year our paper describing these epigenetic modifications on the inactive X had come out in Cell and that was really the beginning of my career in epigenetics. I came back to France in 2001 and set up my lab at the Curie, looking at the role of epigenetic modifications and X-chromosome organisation during development.

In looking at chromatin organisation on the X, your lab was one of the first to describe topologically associating domains. Can you explain what these are and why they are important – both in the context of X inactivation and more broadly?

So this comes back to my early postdoc work – trying to understand why these large transgenes wouldn't function as an Xic in single copies. I was convinced that they must be missing key elements – either enhancers or nuclear localisation anchors, and figuring out what these were kind of became my 'holy grail'. Around 2007, I heard Job Dekker give a talk about chromosome confirmation capture techniques, showing that you could use these to detect long-range enhancers and local chromosome organisation. I talked to a PhD student in the lab, Elphège Nora, about Job's work and we realised that using the 5C (carbon copy chromosome conformation capture) technique, he could find out what was missing in the transgenes. So he went and learned the techniques in Job's lab, came back, repeated the experiments many times and kept picking up these megabase chunks of DNA that tended to interact with each other preferentially over their neighbouring sequences. We saw these interactions in different cell types – the shorter range interactions would change from one cell type to the other, but the basic partitioning into these large domains was quite conserved during differentiation. So we called them 'topologically associating domains' or TADs.

At this point, we weren't sure what was going on with our transgenes. Thanks to 5C we could see that the Xic comprises at least two TADs: the promoter for the *Xist* gene, which triggers X inactivation, lies in one TAD of about 500 kb; and its antisense regulator lies in another TAD of about 300 kb. So the minimum region for the Xic is about 800 kb – no wonder our constructs never worked! At the same time, we were looking at transcriptional dynamics during differentiation at very high time resolution, and saw that genes within TADs showed coordinated expression – the transcriptional dynamics superimposed on the TAD structure fitted very well. And this is essentially one of the things that we think TADs may be doing: in some regions of the genome, they may help to coordinate the dynamics of transcriptional regulation.

The term 'epigenetics' is very loosely used, with meanings ranging from 'chromatin marks' through to 'transgenerational effects'. How would you define epigenetics?

Used and abused! I used to get quite upset about this, because 'epigenetics' is often conflated with environmental impact on heritability, and I would find that members of the public would associate epigenetics with questions around what happens if, for example, someone stresses a pregnant mother – does that transmit epigenetic changes, depression and so on, to her child and grandchildren? But to me, this wasn't epigenetics. I thought of epigenetics in the way that Riggs and Holliday defined it: changes in gene expression or genome function that are heritable (through mitosis or meiosis) but not due to changes in the DNA sequence.

However when you look at the history of the field, you realise that Waddington – who coined the word – defined it as 'genotype meets phenotype' i.e. how the action of genes through development leads to particular phenotypes. This is a much broader definition, so I can understand why, to some people, epigenetics can be considered as the influence of the environment. These days I think it is sometimes used in an even narrower way than the Riggs and Holliday definition – in that the changes have to be chromosome or chromatin associated. So I've become more relaxed about it now, but I do think that when you talk about epigenetics, you really have to define what you mean by it.

A few years ago, you co-organised a Company of Biologists workshop on 'transgenerational epigenetic inheritance', and you've said publicly that there's too much hype around this topic – particularly given the paucity of solid evidence in mammals. To what extent do you think traits might be inherited across generations and how could it happen?

Clearly, there are transgenerational epigenetic effects – heritable phenotypes that are not associated with changes to the DNA – in many systems, including mammals. What I would get upset about was the idea of environmentally induced epigenetic transgenerational effects. For sure, there are intergenerational effects, where, for example, a foetus (and even the germline of that foetus) might suffer if a mother is malnourished. But to go from this to saying that these changes can be transmitted across many generations (once the initial signal has gone) is premature, I believe. I still don't think there's any really sound evidence for it in mammals. In other animals, like *C. elegans*, the evidence for this is quite strong though.

On the other hand, it's clear that there are genomic sequences that somehow avoid reprogramming. So I'm sure that there are bits of our genome that become epigenetically marked and avoid the reprogramming that happens in the germline or in the fertilised egg. The question is: do they have any phenotypic impact, do they matter? Things are moving fast in the field, and it's becoming increasingly clear that a lot of these not fully reprogrammed 'epi-alleles' in mammals are associated with so-called 'junk' DNA (repeats, transposable elements), and that there may be both genetic and epigenetic changes induced by the environment. A lot of recent data also point to non-chromatin-based transmission via RNAs, particularly in the context of metabolic phenotypes. It is exciting that we at last have the tools to detect the molecules that could be carriers of trans-generational information and really see how much of this happens in different organisms.

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After many years at the Institut Curie, you're now taking up the position of Director General at EMBL in Heidelberg. What excited you about the prospect of moving to EMBL, and what do you hope to achieve in this position?

I think EMBL is almost unique in the world for trying to do biological research at the molecular level in the most ambitious way possible. Their mission is to bring in young intelligent people, let them explore whatever they're interested in and happens to be possible and exciting at the time, and provide the resources and develop the technologies to support their work. This enables important discoveries to happen and trains the next generation of scientists.

Actually, one of the reasons I accepted this new job was Brexit. It was just after the Brexit vote that I was contacted to see if I'd be interested in the EMBL position. I'd spent several months complaining bitterly to anyone who would listen about the impact of Brexit on science, the problems with funding basic research and so on – I was becoming a bit of a whinger. It also happened that I was about to step down as Director of my unit at the Curie; I was looking forward to focusing only on my lab, and really wasn't looking at all for another position as a director of something. But Director General of EMBL is not just any old job and EMBL is not just any old organisation – it represents a model for European science. At the Institut Curie, Daniel Louvard (who was Director there when I joined and an EMBL alumnus) had remodelled the Institute as it is today, based on EMBL – junior groups, turnover, not much hierarchy, bringing in the best technology and sharing it among all the people so that everyone gets to do excellent science. And we'd all really thrived in that atmosphere, so when they called me about the EMBL position, I thought that, rather than complaining about everything, I should take the opportunity to do something positive!

In terms of what I want to do, EMBL is currently in the middle of a 5 year plan, which is called 'Digital Biology': the idea is to go all the way from the molecule to the organism, taking an integrative approach – using genomics, proteomics, imaging and so on – to understand organisms. One of my visions is to move this to the next level – into what we can broadly call ecosystems. I feel that we finally have the tools to go all the way from the molecule to the population or the ecosystem, using molecular approaches. This of course goes from bacteria to humans. I'm interested in things like molecular evolution, the influence of the microbiome, using multiple technologies to understand how organisms respond to environmental change. One of the projects that inspired me was Tara Oceans, which Eric Karsenti had spearheaded 10 years ago when he was at EMBL. Of course, this is way out of my comfort zone, but Eric told me the same was true for him before he started the Tara project – he was just a cell biologist who liked sailing!

You'll be EMBL's first female Director General. To what extent do you see yourself as a role model for women in science?

I think I've been pretty lucky through my career in that I've been surrounded by a lot of very supportive people, including men who are perhaps even more militant feminists than I would be myself. My field, X inactivation, was essentially founded by a woman (Mary Lyon), and there are lots of prominent women in the epigenetics field, so I had all these role models without really thinking about it.

But as I gained more responsibilities, I would go to meetings and notice that I was the only woman in the room. That's when I started to realise all the clichés are true – you sometimes have to talk twice as loudly to get heard, to keep repeating yourself to make your point. I do think things are changing for the better, but I realise that a lot of young women still shy away from science for many reasons.

Female students and postdocs in my lab often ask me how I did it – how do I deal with kids and work and so on? I tell them not to spend too much time thinking or calculating, just do what you feel is right and you'll find a way. Actually, I find that women (including myself!) become even more efficient in the lab after they have kids. But honestly, I never calculated my career or my life, I just took the path that felt right, for my science and for my personal life. So I guess this is the kind of role model I want to be – to prove that you don't need to think through every step but go where your heart takes you.

I'd like to see more female PIs at EMBL. In my department at the Curie, we're 50-50, without having to worry about it. I think women can be put off from male-dominated institutes; once you get to a critical mass, it's easier to attract women. I think that very subtle things can help improve gender balance: giving the right encouraging signs, dealing with issues around partners and kids, convincing women (who can often be more insecure) that they can go for that next position or whatever. Everyone needs someone to give them a nudge sometimes to help them succeed.

Finally, is there anything Development readers would be surprised to find out about you?

I don't know if this is surprising, but I don't want to carry on doing science until I crumble: I'm kind of looking forward to retirement. If, for whatever reason, I had to give up science today, I'd be ok with that – I'd find other things to throw myself into. Right now, I'm co-president of a program called 'Pause' in France, which was set up to help scientist refugees. We're helping scientists in exile who come in to France from countries in danger – from places like Syria, Iraq and Turkey. I help evaluate proposals, and hardly any of them come from biologists – it's more about archaeologists, geographers, social scientists. When I read these proposals, it's incredible: you see how a human life can be totally transformed or destroyed from one day to the next. In addition to the destruction of science by wars, in some countries people who sign a petition, or speak openly about politics, can be arrested or chased out of their universities. They have to pack up their labs and families, and move elsewhere, leaving their science behind. Partly through this work, I've realised that I really care about freedom, and I'm really interested in people. And right now, there's a lot to do – so if I had to stop doing science, I'd like to think I could be useful in that area.