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Editor Profile: Eric Chevet

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Abstract

In this special interview series, we profile members of *The FEBS Journal* editorial board to highlight their research focus, perspectives on the journal and future directions in their field. Eric Chevet is Research Director at the French National Institute of Health (INSERM) and Director of the INSERM Unit U1242 “Oncogenesis, Stress, Signaling” in the Comprehensive Cancer Centre Eugène Marquis at the University of Rennes. He has served as Editorial Board Member of the FEBS Journal since 2019.

Can you give an overview of your research group’s major focus and goals?

The group is investigating how perturbation of endoplasmic reticulum (ER) homeostasis can play an important role in cancer development. We explore the function of this sub-cellular compartment from a molecular and cellular perspective by studying the adaptive pathways triggered when ER homeostasis is disrupted (the Unfolded Protein Response, UPR). Then, we translate those findings into the understanding of disease development, more specifically cancer, in order to identify actionable mechanisms. Finally, we use the knowledge we have built to design tools that target the components of the UPR with therapeutic objectives. Our research projects are highly collaborative and allow us to interact with researchers from fields other than biology (*e.g.* chemists, computational scientists) and with clinicians. The latter interactions, which are instrumental for our research process, are catalyzed by the fact that the laboratory is located within the Comprehensive Cancer Centre Eugène Marquis in Rennes.

From a broad point of view, why is it important to delve into these research questions?

The ER is the first compartment of the secretory pathway and also the most abundant organelle in eukaryotic cells. Additionally, it plays a key role in cellular adaptation to various stresses that lead to protein homeostasis disruption; this protective mechanism is highly challenged in cancer cells. The understanding and characterization of the molecular and cellular mechanisms by which the ER achieves these functions is not only interesting from a fundamental, cell biology perspective but also because these mechanisms may represent actionable tools that are applicable in pathological conditions such as cancer or inflammatory diseases.

What’s been your favourite (personal) breakthrough, to date? How did you feel when you made this discovery and realized the wider implications?

I would be tempted to say the next one, but, besides the joke, I would name two articles that notably opened up research fields in our laboratory. Both stories were published in the *Journal of Biological Chemistry*, in 2004 and 2011 respectively. The first study demonstrated that the protein tyrosine phosphatase PTPN1 is necessary to achieve IRE1-mediated XBP1

mRNA splicing. This work connected for the first-time tyrosine kinase/phosphatase signaling to the UPR and in particular to the IRE1 branch. After a long search for the mechanisms underlying this observation, we finally figured out that the connection occurred through the RNA ligase acting together with IRE1, named RTCB, to achieve XBP1 mRNA splicing (Papaioannou et al. 2022). Our 2011 milestone paper describes the discovery of the Protein Disulfide Isomerase AGR2 as an ER-resident, nascent chain binding protein involved in protein folding and ER quality control (Higa et al. 2011). Subsequent studies allowed us to further document the role of AGR2 and its gains of extracellular and cytosolic functions (Fessart et al. 2016, Maurel et al. 2019, Sicari et al. 2021), leading to the development of potential therapeutic antibodies.

What research thread in your lab are you currently most excited about?

At the moment, the thread that excites me the most is our attempt to understand how the signaling of the UPR (and that of its IRE1 arm more particularly) intersects with other cellular signaling pathways (*e.g.* tyrosine kinases). We are focusing our attention on the reciprocal signaling existing between the UPR and other pathways, on tissue/cell specificities of such phenomena and on the impact these signaling characteristics could have in cancer development.

What are the key ongoing challenges in your field and can you discuss ways that these might be addressed?

From a general perspective, I think that organelle biology has reached an age of maturity and now one key challenge will be to provide a comprehensive and integrated view of their functions in physiology and pathology. Of course, the ER is part of the game. To tackle this question, it is likely that approaches based on spatial deconvolution (even at the single-cell level) of organelle morphology (relationship between organelle structure and function), composition (for example, proteins, lipids,) or interactions with other cellular structures will provide relevant data. If those are combined with dynamic analyses in normal and disease conditions, it could be possible to reach a subcellular map of the cell and understand its contribution to physiological and pathological mechanisms, and perhaps find ways to alter those as therapeutic approaches.

Have you always been interested in science and was it inevitable that you would end up in this career? Were there any particular events, influences or mentors that shaped your research direction?

I have always been interested in trying to understand things; however, I really got into biology (relatively) late, when I attended a course on cellular and molecular biology at the Pasteur Institute as a Master's student. Even later, I became fascinated by the ER during my post-doc with John Bergeron at McGill University. Since then, I have kept trying to contribute to the characterization of this organelle's functions by working with a team of very talented researchers in the laboratory and with highly enthusiastic collaborators.

How do you balance management of your research group with your other academic and professional commitments?

The research developed in the team is what is keeping me afloat and I am trying to privilege exchanges with my group and with colleagues in the Institute by sanctuarizing my time as much as possible. Regarding my other academic and professional commitments, organization -including the preparation of time-based to-do lists and good planning are key.

What advice can you offer an early-career researcher who is hoping to forge a successful career in academia?

Keep doing what you are loving (as much as possible), define precisely the scientific question you want to address (interest, relevance, impact), be patient, persistent and curious. It's also important to remain open to opportunities, to not hesitate to collaborate and get advice from people with more experience, and to try to plan ahead and think about where you would like to see yourself in a couple of years.

How were you persuaded to join the Editorial Board of *The FEBS Journal*? In what ways do you think that the journal stands out from other journals in the Biochemistry & Molecular Biology sector?

The FEBS Journal Editor-in-Chief, Seamus Martin, played an instrumental role in this. *The FEBS Journal* has always belonged to the biochemistry journals I like to read (even since it was still the *European Journal of Biochemistry*), together with the *Journal of Biological Chemistry* and the EMBO family of journals. So, when Seamus asked me if I would be interested in joining *The FEBS Journal* Editorial Board, I gave him a positive answer right away. I believe that society journals such as *The FEBS Journal* are of great importance to the community as they are run by scientists who understand what the challenges are for authors. Moreover, as part of the Federation of European Biochemical Societies, the journal advertises its European roots beyond the frontiers of the EU and disseminates high-quality science.

Do you have a favourite *The FEBS Journal* paper? (you can't choose one of your own!)

In fact, I have more than one. On the one hand, I really enjoyed reading a Special Issue coordinated by Stefan J. Marciniak on 'ER stress in Disease' which very broadly covers the topic (Marciniak, 2019). We had the opportunity to contribute a manuscript to this series with a group of 14 students that were part of an EU H2020 Innovative Training Network (ITN) Marie Curie. It was a very fun experience to coordinate their work. On the other hand, I will pick a research article from the von Heijne laboratory (Monné et al. 2005), which describes the kinetics of translocation across ER membranes of transmembrane segments in the multi-spanning protein ELOVL3. I like this article as it illustrates very well how simple and refined biochemical approaches can tackle particularly complex mechanisms (in the ER).

What long-lasting impact will the COVID-19 pandemic have on science and the public's perception of it, in your view?

Even though the global impact of the COVID-19 pandemic remains hard to predict, in my opinion there are several aspects that we can already consider, including the observation of an unleashed mobilization of the scientific community and its capacity in such a short time to come up with efficiently applicable solutions (vaccines). The downside of this is the uncontrolled/unexploitable proliferation of scientific articles (>230000 articles in Pubmed - keywords SARS-Cov2 or Covid-19 in two years). It is also the first time in history that a pandemic of this amplitude has been so widely documented from molecular to social aspects

in real time. This will create an immense resource for future research and also (hopefully) help in designing efficient decision-making policies in case anything similar happens again.

Tell us something about yourself that we might be surprised to hear!

I love outdoor activities, including hour-long bike commuting to work or week(s)-long hikes in the wild. These not only represent a nice way to clear your mind before or after work and wash up negative thoughts, but also teaches you to manage your motivation and cope with the unexpected – important assets in science!