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INTERVIEW

The people behind the papers – Paul Huber and Carole LaBonne

The bromodomain and extra-terminal (BET) family of proteins reads epigenetic histone acetylation marks on the genome and regulates the transcriptional machinery. In their study, Carole LaBonne and colleagues reveal the role of BET protein activity in the maintenance of pluripotency and establishment of the neural crest in *Xenopus laevis*. To know more about their work, we spoke to the first author Paul Huber and the corresponding author Carole LaBonne, Developmental and Stem Cell Biologist at Northwestern University.

Carole LaBonne (left) and Paul Huber (right)

Carole, what questions is your lab trying to answer?

CL: Work in my lab at Northwestern University focuses on two very important stem cell populations – the embryonic stem cells (ESCs) found in blastula stage embryos and neural crest stem cells. Both of these cell types are found only in vertebrate embryos and understanding how they arose is crucial to understanding how vertebrates, including humans, evolved. We want to understand how their developmental potential is maintained and their transition to lineage restricted states is controlled. *Xenopus* is a fantastic system for such studies. The embryos are really large, develop rapidly and provide copious material for genomics studies. Also, the pluripotent blastula stem cells can be easily explanted and induced to give rise to any cell type, and they lineage restrict on the same time scale – approximately 7 h – that the cells normally do *in vivo*. *Xenopus* embryos are also ideal for rapid gain- or loss-of-function studies, including CRISPR-mediated genome editing, and the fate of every early embryonic cell has been mapped. We are very fortunate to be able to take advantage of the wonderful resource center for this model, the National Xenopus Resource (NXR), which generates and distributes transgenic lines and CRISPR mutants to the community as well as to have Xenbase, one of the most comprehensive data-rich model organism databases in the world.

Tell us about the background of the field that inspired your work

CL: Our lab was the first to show that Myc was required for neural crest formation, implicating this transcription factor in control of stem cell attributes, several years before its role in induced pluripotency was described by Yamanaka and colleagues. This led to our interests, which are ongoing, in the control of stem cell attributes more generally. We were the first to report that most other factors implicated in controlling pluripotency in blastula ESCs are also expressed in neural crest cells and required for their genesis. Moreover, the reverse is true as well – components of the neural crest gene regulatory network (GRN) are expressed and required in pluripotent blastula cells. As the retention of this GRN activity is likely what allowed neural crest cells to evolve, we have been actively dissecting how this happens, including epigenetic contributions.

Can you give us the key results of the paper in a paragraph?

CL & PH: We had previously found that control of histone acetylation is important for both blastula-stage pluripotency and neural crest development: that raised the key question of what reads these acetylation marks and what consequence that has for gene expression in these stem cell populations. In the current study, we show that BET family proteins, a class of epigenetic factors containing bromodomains that target acetylated lysines, are essential readers in these stem cells. We show that inhibiting BET activity in early *Xenopus* embryos leads to loss of pluripotency in blastula stem cells and loss of neural crest formation. Surprisingly, this meant that blocking the activity of a reader of acetylation leads to the same phenotype at a functional level as the loss of histone deacetylase (HDAC) activity, which increases histone acetylation. To further characterize the mechanisms through which these two inhibitors regulate pluripotency, we compared the transcriptome changes elicited by HDAC and BET inhibition in blastula stem cells, which showed that these functional outcomes were achieved by distinct mechanisms. We gained further insight into the role of BET activity in controlling stem cell attributes by examining the effects of BET inhibition on explants reprogrammed to a neural crest progenitor state or adopting an epidermal fate. This analysis showed that inhibition of BET activity in neurula-stage explants led them to adopt a transcriptomic state with shared features of both pluripotent blastula cells and neural progenitor cells, regardless of the initial lineage transition (epidermal versus neural crest). This raised the intriguing possibility that blocking BET activity might extend the competence of initially pluripotent cells to lineage inducing cues that is normally lost during gastrulation and, indeed, we found that inhibiting BET activity prolonged the competence of cells to transit to a neural progenitor state.

Paul, when doing the research, did you have any particular result or eureka moment that has stuck with you?

PH: We were totally blown away by the initial observation that blocking BET activity in whole embryos had a much more dramatic impact on the formation of neural crest cells than it did on other cell lineages present at neurula stages. Also, the realization that the functional consequences of blocking the activity of a reader of acetylated lysine was overtly the same as blocking the activity of an eraser of those marks. That finding really drove the genomic parts of the study.

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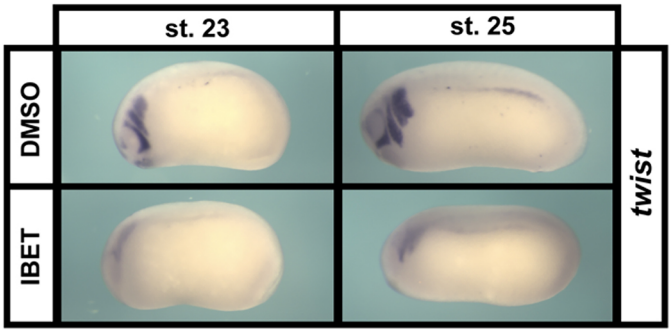

Inhibition of BET activity leads to a dramatic loss of neural crest cells as visualized by *twist* expression.

Paul, and what about the flipside: any moments of frustration or despair?

PH: I definitely encountered some frustration collecting samples for RNA-seq, which required robust neural crest induction and clean RNA isolations across many conditions.

Why did you choose to submit this paper to Development?

CL & PH: This study follows up on a previous study focused on epigenetic regulation of these two stem cell populations that was also published in Development, so we knew it would be a good fit for the journal. Also, Development is scientist-led, and it is one of the journals we rely on to keep up with important work in the field.

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Carole, where will this story take your lab next?

CL: We are part of the newly launched National Institute for Theory and Mathematics in Biology (NITMB; www.nitmb.org) that is jointly funded by the National Science Foundation and the Simons Foundation. Our goal going forward is to better understand the emergent properties of the GRNs and embryos more generally using approaches such as dynamical systems modeling. NITMB is a fantastic resource that hosts workshops, long-programs and a visiting scholar program that anyone can apply to, and it also has an independent Post-Doctoral Fellows program. I hope people will check it out and hopefully visit.

Finally, let's move outside the lab – what do you like to do in your spare time?

PH: I really enjoy a lot of outdoor activities like fishing, camping and kayaking/boating. I also love cooking, as well as attending various concerts/shows/plays/musicals.

CL: Promoting the field of developmental biology and supporting a diverse next generation of scientists is really important to me, and that takes up a good chunk of my 'spare' time. As the incoming President of the Society for Developmental Biology (SDB), I am really proud of the efforts the society makes on this front, for example the 'Choose Development' summer research program for undergrads is really impactful. I am also excited to be co-organizing the 20th International Congress of Developmental Biology in San Juan, Puerto Rico, next June – it is shaping up to be a fabulous meeting.

Reference

Huber, P. B., Rao, A. and LaBonne, C. (2024). BET activity plays an essential role in control of stem cell attributes in *Xenopus*. *Development* **151**, dev202990. doi:10.1242/dev.202990