galaxies similar to JADES-GS-z7-01-QU go through cycles of intense star formation before quickly becoming quenched. During this process, each successive burst is less disruptive than the previous one, as these galaxies grow their stellar mass and sustain equilibrium between gravity and energetic gas expulsion for longer periods. This means that low-mass galaxies such as JADES-GS-z7-01-QU are quenched only temporarily: they are said to be mini-quenched.

The detection of JADES-GS-z7-01-QU marks the first time that a galaxy has been observed in this mini-quenched phase at such early epochs. Although the exact physical mechanisms responsible for temporary quenching are still unknown, Looser and colleagues' spectral modelling offers some clues. The inferred star-formation history suggests that the event that quenched this galaxy was abrupt. This, in turn, implies a mechanism that ejected gas from the galaxy much faster than it could be replenished.

Supernovae have been shown to do this in low-mass galaxies, but simulations[11] suggest that they are not energetic enough to quench a galaxy with JADES-GS-z7-01-QU's stellar mass. More-powerful mechanisms, such as accreting (growing) supermassive black holes, have been observed in nearby low-mass galaxies[12], but there are no signatures of such objects in the galaxy's spectrum. However, it could be that the radiation from an accreting black hole is heavily obscured by dust, which is common in the earliest galaxies[13].

Looser and colleagues' discovery of JADES-GS-z7-01-QU is undoubtedly exciting, but it leaves us with more questions than answers. Simulations predict that the first mini-quenched galaxies were quenched as early as 600 million years after the Big Bang[10,11,14], which suggests that more will be found now that JWST has given astronomers the technological capabilities to do so. Looser *et al.* have paved the way for statistical studies of this intriguing population. Indeed, since these results were first made public, three more distant mini-quenched galaxies have been discovered[15], including two by members of the same research group as Looser and co-authors[16].

Looking ahead, dozens of candidate galaxies await spectroscopic confirmation with JWST (for example, those studied in refs 8, 9, 16). Growing the pool of mini-quenched samples will be crucial for calibrating models that simulate how galaxies become quenched. The hunt for the earliest quenched galaxies is on.

Jacqueline Antwi-Danso is in the Department of Astronomy & Astrophysics, University of Toronto, Toronto, Ontario M5S 3H4, Canada.
e-mail: j.antwidanso@utoronto.ca

1. Baldry, I. *et al. Astrophys. J.* **600**, 681–694 (2004).
2. Looser, T. *et al. Nature* **629**, 53–57 (2024).
3. Valentino, F. *et al. Astrophys. J.* **889**, 93 (2020).
4. Oesch, P. *et al. Astrophys. J.* **709**, L16–L20 (2010).
5. Poggianti, B. M. & Barbaro, G. *Astron. Astrophys.* **325**, 1025–1030 (1997).
6. Anglés-Alcázar, D. *et al. Mon. Not. R. Astron. Soc.* **470**, 4698–4719 (2017).
7. Tacchella, S. *et al. Mon. Not. R. Astron. Soc.* **457**, 2790–2813 (2016).
8. Asada, Y. *et al. Mon. Not. R. Astron. Soc.* **527**, 11372–11392 (2024).
9. Endsley, R. *et al. Mon. Not. R. Astron. Soc.* **524**, 2312–2330 (2023).
10. Dome, T. *et al. Mon. Not. R. Astron. Soc.* **527**, 2139–2151 (2024).
11. Gelli, V. *et al. Astrophys. J.* **954**, L11 (2023).
12. Davis, F. *et al. Mon. Not. R. Astron. Soc.* **511**, 4109–4122 (2022).
13. Harikane, Y. *et al. Astrophys. J.* **959**, 39 (2023).
14. Lovell, C. *et al. Mon. Not. R. Astron. Soc.* **525**, 5520–5539 (2023).
15. Strait, V. *et al. Astrophys. J.* **949**, L23 (2023).
16. Looser, T. J. *et al.* Preprint at https://doi.org/10.48550/arXiv.2306.02470 (2023).

The author declares no competing interests.
This article was published online on 24 April 2024.

Developmental neuroscience

Early origin of vertebrate sympathetic neurons

Uwe Ernsberger & Hermann Rohrer

The sympathetic nervous system, which enables the fight-or-flight response, was thought to be present only in jawed vertebrates. Analysis of a jawless vertebrate suggests that this system might be a feature of all animals with a spine. **See p.121**

One of the key innovations that arose in vertebrates was the evolution of a branch of the nervous system called the sympathetic nervous system. This forms from cells produced by stem cells that originate in a structure called the neural crest. The sympathetic nervous system is associated with the fight-or-flight response and the neurotransmitter signalling molecules adrenaline and noradrenaline. On page 121, Edens *et al.*[1] report that this system is not found solely in jawed vertebrates, and that the basic building blocks and developmental regulators of a sympathetic nervous system are also present in the jawless vertebrate fish the sea lamprey (*Petromyzon marinus*).

"The time course of neuronal differentiation in sea lampreys is surprisingly slow."

This discovery refines the understanding of the nervous system and how it functions in a vertebrate closely related to the earliest known vertebrates. This landmark study uncovers a characteristic molecular and developmental 'fingerprint' present in noradrenaline-producing (noradrenergic) sympathetic neurons in sea lampreys that is found across many classes of vertebrates, from jawless fishes to mammals (Fig. 1). Studies from the nineteenth and into the twentieth century culminated in the shared opinion that the jawless fishes are not equipped with an 'organized' sympathetic nervous system[2] – represented by structural hallmarks such as a chain of clustered neurons called sympathetic ganglia.

However, the availability of methods to explore gene expression has provided data that revises the old view and establishes the sympathetic nervous system as a pan-vertebrate feature. Edens and colleagues' work completes the search for the evolutionary onset of the principal components of the vertebrate autonomic nervous system – the part of the nervous system (including the sympathetic nervous system) that regulates involuntary processes that are essential for survival. This study marks a milestone in this field of research, the implications of which range from understanding the generation of cell identities across evolutionary time scales to the development of anticancer therapeutics in accessible model organisms.

Edens *et al.* present a detailed picture of the developmental expression of key transcription factors and functional signature genes that are characteristic of sympathetic neurons. The method of *in situ* hybridization chain reaction reveals that transcripts encoding Ascl1, Phox2 and Hand, related to three evolutionarily conserved transcription factor proteins, Ascl1, Phox2b and Hand2 (which are known to be important for sympathetic neuron development in jawed vertebrates) are co-expressed in the same cells in the sea lamprey. These transcription factors were also co-expressed with genes that encode the enzymes tyrosine hydroxylase and dopamine β-hydroxylase, which are involved in the synthesis of noradrenaline.

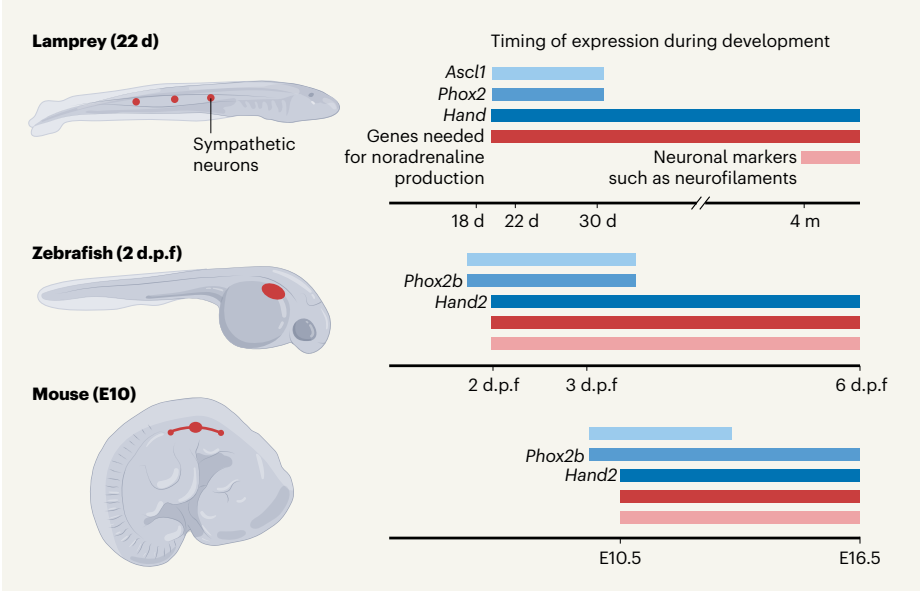

Figure 1 | Sympathetic neurons in different types of vertebrate. Edens *et al.*[1] report that these neurons (associated with the fight-or-flight response) are not found solely in jawed vertebrates but are also found in the jawless vertebrate sea lampreys (*Petromyzon marinus*). Red indicates the sites in the developing embryos at which sympathetic neurons first differentiate. Genes encoding the transcription factor proteins Ascl1, Phox2 (Phox2b in jawed vertebrates) and Hand (Hand2 in jawed vertebrates) are needed for sympathetic neurons to develop. When these neurons form, they express enzymes (such as tyrosine hydroxylase) that produce the neurotransmitter molecule noradrenaline. These neurons also express components (such as the protein synaptotagmin 1), which function in the neurotransmitter-containing vesicles. In sea lampreys, the neuronal differentiation associated with the production of characteristic neuronal components such as structures called neurofilaments occurs relatively late in development compared with the case of jawed vertebrates, such as zebrafish (*Danio rerio*) or mice. Data from refs 1, 4, 5, 7, 8 and 11. Sea lampreys hatch after 10–13 days of embryonic development and form larvae at 33–40 days. Zebrafish hatch after 48 hours and become early larvae at 72 hours. They reach juvenile stages by 30–40 days and reach sexual maturity within 2.5 months. Mice reach a mid-embryonic stage by 10 days, are born at 19 to 21 days and reach sexual maturity by around 40 days. D, day of development; E, day of embryonic development; d.p.f., days post-fertilization; m, months.

Cell tracing by dye labelling revealed that the cells that express tyrosine hydroxylase are derived from a migratory population of cells that are initially located in the spinal cord and that differentiate into a nerve cord between the intestine and a structure called the notochord. RNA sequencing of cells that express tyrosine hydroxylase in the nerve cord demonstrated a gene-expression pattern remarkably similar to the pattern found in mouse sympathetic neurons[3]. The genes encoding tyrosine hydroxylase, dopamine β-hydroxylase and the enzyme DOPA decarboxylase (which is also involved in the synthesis of noradrenaline) were found to be highly expressed with several genes encoding proteins that function in vesicles that are associated with synapses (connections between neurons). These vesicular proteins include vesicular monoamine transporter 2, which packages neurotransmitter molecules into vesicles, and the proteins synaptotagmin 1, SNAP-25 and syntaxin 12 — essential for the fusion of vesicles with the cell membrane that enables the regulated release of stored neurotransmitter. Components characteristic of neurons, such as neurofilaments, were detected in mature neurons.

The developmental transition that occurs when neural-crest-derived progenitor cells mature to differentiated neurons is still not fully understood. In mice and birds, it is a rapid process in which the initial noradrenergic and neuronal differentiation occur in parallel within one day of embryonic development (Fig. 1). However, the time course of neuronal differentiation in sea lampreys is surprisingly slow by comparison, and has similarities to the delayed generation and asynchronous differentiation of structural components of the sympathetic nervous sysyem (trunk sympathetic ganglia) in zebrafish (*Danio rerio*)[4]. Phox2b has an essential role in the differentiation process of structures such as the trunk sympathetic ganglia. This transcription factor is a key regulator of autonomic neuron development in mice, chick and zebrafish[5–7], and it controls the expression of a range of neurotransmitter-specific and general neuronal characteristics. Hand2 selectively affects noradrenergic differentiation in zebrafish[8] and it is possible that Hand is implicated in this function in sea lampreys. This evolutionary conservation of developmental processes might offer a unique opportunity to study a

From the archive

William Bateson surveys the previous century of biology, and an innovative proposal to stop exam over-preparation.

100 years ago

An address on progress in biology during the last hundred years has one element of simplicity; since ... the whole subject from its inception may be held included. Though the materials studied by biologists are those which have been the objects of ... curiosity from the earliest times, yet the biological way of looking at them was new, and biology was a term deliberately selected to proclaim the consciousness of a new hope. Treviranus—Gottfried Reinhold, 1776–1837, of Bremen ... was the first to use the word *Biology* (1802). He complained that ... zoology and botany were lacking ... in comprehensiveness ... [C]atalogues of plants and animals ... are a beginning, not an end ... If ... one objects that he is offering old things in a new form ... he claims that to see them in the new form is no trifling help ... The new word connoted a new thought.

From *Nature* 3 May 1924

150 years ago

[A]t the ceremony of capping the Graduates in Arts of Edinburgh University, Prof. Tait gave an address ... On the subject of "Cram" he spoke as follows:

— "[E]xamination ... is ... about the most imperfect of human institutions ... [I]n too many cases it is not only misleading, but directly destructive, especially when proper precautions are not taken to annihilate absolutely the chances of a candidate who is merely crammed, not in any sense educated ... There is ... so far as I can see, only one, way of entirely extirpating cram as a system ... Take your candidates, when fully primed for examination, and send them off to sea — without books, without even pen and ink; attend assiduously to their physical health, but let their minds lie fallow. Continue this treatment for a few months, and then turn them suddenly into the Examination Hall. Even six months would not be wasted ... if it really enabled us to cure the grand inherent defect of all modern examinations."

From *Nature* 30 April 1874

type of tumour called a neuroblastoma using the zebrafish as a model organism[9].

Comparative analysis of sympathetic neuron activity in response to different stimulation settings has firmly established the existence of sympathetic pathways that are specific to different tissues in different organs of the body and the differential control of activity outflow to diverse targets[10]. Developmental studies and single-cell analyses of gene expression in mice have identified a range of sympathetic neuron populations that are associated with distinct cardiovascular, thermoregulatory and maternal functions. These have different gene-expression patterns and distinct requirements for growth-factor proteins during development[3].

Edens and colleagues' observation of the co-expression of the gene encoding tyrosine hydroxylase and the gene encoding the neuropeptide NPY in sea lamprey sympathetic neurons provides evidence for the existence of a neuron population that is comparable with that of an abundant noradrenergic population in mice, called NA3. This population is characterized by NPY expression that is representative of vasoconstrictor neurons that regulate blood-vessel diameter and resistance. The authors' discoveries point to a remarkable diversification of sympathetic neuron populations among vertebrate classes and species. The findings also prompt questions about the selective pressures and genomic mechanisms that underlie this evolutionary outcome across the tree of life, such as those that lead to the crucial involvement of the sympathetic nervous system in thermoregulation in birds and mammals.

One key unanswered question in the current study is whether the neurons with key noradrenergic sympathetic features are connected to the central nervous system through neurons known as preganglionic sympathetic neurons, as is the case for jawed vertebrates. The anatomical targets of the sympathetic neurons in sea lampreys and their role during the life cycle of the fish also remain to be determined. In the context of development, it will be interesting to establish how the late acquisition of neuronal characteristics and proliferative activity in neural-crest-derived cells are regulated. This study underscores questions of how transcriptional circuits that are specific to autonomic neurons are established early in vertebrate development, how sympathetic circuitry became organized during vertebrate evolution, and how this circuitry might adapt to the physiological, in particular thermoregulatory, challenges that animals will face as a result of a changing climate in the future.

Uwe Ernsberger and **Hermann Rohrer** are at the Institute for Clinical Neuroanatomy, Goethe University, 60590 Frankfurt, Germany.
e-mail: ernsberger@outlook.de

1. Edens, B. M., Stundl, J., Urrutia, H. A. & Bronner, M. E. *Nature* **629**, 121–126 (2024).
2. Rovainen, C. M. *Physiol Rev.* **59**, 1007–1077 (1979).
3. Furlan, A. *et al. Nature Neurosci* **19**, 1331–1340 (2016).
4. An, M., Luo, R. & Henion, P. D. *J. Comp. Neurol.* **446**, 267–275 (2002).
5. Pattyn, A., Morin, X., Cremer, H., Goridis, C. & Brunet, J. F. *Nature* **399**, 366–370 (1999).
6. Stanke, M. *et al. Development* **126**, 4087–4094 (1999).
7. Pei, D. *et al. PLoS Genet*. **9**, e1003533 (2013).
8. Lucas, M. E., Müller, F., Rüdiger, R., Henion, P. D. & Rohrer, H. *Development* **133**, 4015–4024 (2006).
9. Wertman, J. N. & Berman, J. N. *J. Clin. Invest.* **133**, e167824 (2023).
10. Morrison, S. F. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **281**, R683–R698 (2001).
11. Hirsch, M. R., Tiveron, M. C., Guillemot, F., Brunet, J. F. & Goridis, C. *Development* **125**, 599–608 (1998).

The authors declare no competing interests.
This article was published online on 17 April 2024.

Microbiology

Umbrella toxins join the bacterial arsenal

Sarah J. Coulthurst

Bacteria make protein toxins to compete with other bacteria in microbial communities. A study of a common soil bacterium has revealed a previously unknown type of antibacterial toxin that forms a striking umbrella-like structure. **See p.165**

Within mixed microbial communities, the various bacterial members constantly interact with each other, both cooperatively and competitively. Aggressive competition between bacteria can determine which species prosper in a community and is often mediated by delivery of antibacterial protein toxins from one bacterium to another[1]. On page 165, Zhao *et al*.[2] describe a previously unknown class of self-delivering antibacterial toxins that form a distinctive umbrella-like structure and that might be used by many bacteria in soil and other ecosystems to block the growth of their competitors. This discovery expands the portfolio of mechanisms by which bacteria kill or disable their rivals and offers exciting potential for future exploitation.

Bacteria can use a variety of approaches to harm their competitors. These include the production of diffusible antibiotics and protein toxins, and the direct injection of toxins into neighbouring cells in a contact-dependent manner[1]. Competition is intense in environments in which the microbial community is dense and complex, such as soil and the human gut, and is often fiercest between related bacteria that have similar needs[3].

Many protein toxins involved in interbacterial competition are known as polymorphic toxins, to reflect the existence of multiple versions of the same protein. Polymorphic toxins are large modular proteins that contain varied, exchangeable toxin domains joined to common domains that are required for delivery of the toxin domain from the producer into the recipient 'target' bacterium[4].

Interestingly, many of these toxin domains are found in different polymorphic toxins with unrelated delivery mechanisms. Building on earlier work that used this observation to generate a large data set of predicted polymorphic toxins[5], Zhao and colleagues selected candidate toxins to investigate and chose examples that are found in the ubiquitous soil bacteria *Streptomyces*. These were of particular interest because although *Streptomyces* exist in a competitive soil environment and produce numerous small antimicrobial molecules[6], they had not been previously reported to use polymorphic protein toxins for interbacterial competition.

The authors studied three of the candidate toxins, UmbC1, UmbC2 and UmbC3, in the model bacterium *Streptomyces coelicolor*. Each UmbC protein has a predicted toxin domain at one end and interacts with two other proteins — a specific UmbA and UmbB protein encoded in the same set of genes — to form a protein complex. Three additional UmbA proteins can associate with any of the UmbC-containing assemblies. Structural analysis revealed that Umb complexes form large particles (Fig. 1) with an unusual umbrella-like shape that has not been reported before — hence the name umbrella toxins.

In each toxin-containing particle, UmbC forms a lollipop shape, comprising a ring joined to a long stalk with the toxin domain at the end of the stalk away from the ring. Five 'spokes' extend out from the ring, each containing UmbB and then UmbA, although it was not possible for the authors to determine which of the four possible UmbA proteins was present in which spoke or spokes. Interestingly, each UmbA protein contains a different predicted lectin domain that forms the exposed tip of the spoke. Given that functional lectin domains bind to specific carbohydrates,