Development

Multicellular self-organization

'Hockey or watching the daisies grow' — a drawing by Alan Turing's mother — depicts eleven-year-old Alan staring at daisies while his friends play hockey in the background. This drawing aptly captures Turing's early interest in biology. However, while his work on computation has flourished into modern computers and artificial intelligence, Turing's work in biology began to blossom only recently.

His famous and unique biological paper, entitled 'The chemical basis of morphogenesis', proposed that diffusible substances called morphogens could react together making concentration waves that break the initial symmetry of the embryo. Using reaction-diffusion equations, Turing showed that this was possible via a diffusion-driven instability that amplified small random disturbances to generate periodic spatial patterns. This work was visionary, both technically and conceptually. From a technical point of view, it was the first theoretical biology paper to use computational simulations, which were run on a prototype digital computer at the University of Manchester. Conceptually, it proposed the revolutionary idea that embryogenesis could be entirely a self-organizing process, eliminating the need for external organizational cues in development.

It took many decades for the developmental biology community to accept Turing's idea. This was mainly owing to evidence that embryonic development was controlled by pre-patterns, such as the dorsal organizers found in frogs or the maternal gradients discovered in fruit flies. However, multiple studies to date have demonstrated that embryos have self-organizing and regenerative capacity, and in recent years, 3D stem cell aggregates called embryoids and organoids have highlighted a similar self-organizing potential. Nonetheless, Turing's paper has often been criticized for lacking an intuitive interpretation of how diffusion-driven instability can be implemented in real biological systems. This view, however, ignores that Turing dedicated an entire section to demonstrate that realistic chemical systems were able to undergo diffusion-driven instability and that his paper was published in a time when biology was primarily studied in the light of chemistry. Owing to his premature death, Turing did not have the opportunity to update his model to the genomic era, but the legacy that he left has paved the way in this direction.

Seventy years after its publication, Turing's pioneering paper keeps inspiring researchers and upholds the fundamental concepts behind multicellular self-organization.

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Original article: Turing, A. M. The chemical basis of morphogenesis. *Phil. Trans. R. Soc. London B* **237**, 37–72 (1952)

RNA metabolism

'Poisoning' of the transcriptome by ultraconserved elements

Alternative RNA splicing allows an individual gene to encode functionally distinct RNA isoforms that can differ in stability, localization and protein-coding potential. This key process is regulated by splicing factors (SF), which bind to specific pre-mRNA sequences and enhance or repress splice-site recognition by the core spliceosome. Given their ability to modulate the transcriptome, SF levels are tightly regulated and their dysregulation causes many human diseases. One such complex regulatory mechanism relies on alternative splicing of ultraconserved elements (UCEs) in SF genes themselves.

A set of UCEs in the human genome was first described in 2004; UCEs were defined as regions >200 bp in length with complete sequence homology to rat and mouse genomes. This remarkable evolutionary conservation suggested UCEs have crucial biological roles, yet, intriguingly, UCE deletions in mouse models had no obvious phenotypes.

Interestingly, UCEs are enriched in exons and introns of genes involved in RNA processing and transcription regulation. A set of UCEs in SF genes were termed 'poison exons', corresponding to alternatively spliced non-coding exons that, when included in the mature mRNA, induce nonsense-mediated mRNA decay and thus decrease the abundance of SFs. This process allows for an elegant auto- and cross-regulatory feedback loop, in which the expression of SFs is itself controlled by alternative splicing of poison exons in their own pre-mRNA. However, the role of poison exons in human disease remained largely underexplored, particularly in cancer, even though dysregulation of SF levels had been causally linked with tumour initiation and progression.

Sixteen years later, Thomas et al. (2020) developed the first CRISPR-based method to study the role of poison exons genome-wide. Using a library of paired Cas9 guide RNAs, they systematically excised all poison-exon genomic sequences and thus enabled studying the role of hundreds of mRNA splicing isoforms. In a mouse model of lung adenocarcinoma, the authors interrogated the role in cancer-cell fitness of >550 poison exons and >400 constitutive exons. Their findings revealed that many poison exons act as tumour suppressors by limiting the expression of oncogenic SFs.

This study not only enhanced our understanding of the roles of poison exons in SF regulation, but also provided a tool to systematically characterize splicing isoforms in large scales. Together, these studies have solidified the role of UCEs in shaping the transcriptome.

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Original article: Thomas, J. D. et al. RNA isoform screens uncover the essentiality and tumor-suppressor activity of ultraconserved poison exons. *Nat. Genet.* **52**, 84–94 (2020)

Related article: Bejerano, G. et al. Ultraconserved elements in the human genome. *Science* **304**, 1321–1325 (2004)