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Perspective

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Transposable elements: McClintock's legacy revisited

Cédric Feschotte

Abstract

In 1983, Barbara McClintock was awarded the Nobel Prize in Physiology or Medicine for her discovery of transposable elements. This discovery was rooted in meticulous work on maize mutants that she had carried out 40 years earlier. Over this time frame, our perception of transposable elements has undergone important paradigm shifts, with profound implications for our understanding of genome function and evolution. In commemoration of this milestone, I revisit the legacy of this iconic scientist through the kaleidoscopic history of genetics and reflect on her achievements and the hurdles she faced in her career.

Sections

Department of Molecular Biology and Genetics, Cornell University, Ithaca, NY, USA. e-mail: cf458@cornell.edu

Introduction

Barbara McClintock is often portrayed as an insular character. However, she was in fact a well-recognized figure by the time she discovered transposable elements. During her doctoral and post-doctoral studies at Cornell University in the late 1920s and early 1930s, she worked alongside other prominent maize geneticists such as Marcus Rhoades, Charles Burnham and George Beadle (who would also win a Nobel Prize in 1958). McClintock distinguished herself for combining classical genetics with microscopy techniques that she invented to visualize chromosomes, thereby creating the field of cytogenetics. This powerful approach enabled McClintock to link phenotypes to chromosomal behaviour with unprecedented clarity, yielding fundamental discoveries that we often take for granted today. For example, while still at Cornell as an instructor, she worked with Harriet Creighton, a graduate student she trained informally, to show that meiotic recombination (crossing over) is accompanied by physical exchange between homologous chromosomes[1]. Despite the immediate impact of these findings, McClintock was unable to obtain a research faculty position at Cornell University. Women were generally precluded from research positions at universities, and the Great Depression further reduced job opportunities.

The early years

Between 1931 and 1936, McClintock secured several fellowships to sustain her research and her living. Notably, in 1933, she obtained a Guggenheim fellowship to conduct research in Germany. While her skill set and reputation were growing, McClintock was concerned about the lack of job security. In 1935, she wrote to Burnham: "The uncertainty gets under my skin a bit and hinders my spirits."[2] The horizon brightened in 1936, when she secured an assistant professorship at the University of Missouri. She was 34 years old. There, McClintock focused on the effect of X-rays on chromosome behaviour. By inducing chromosome breakage, she was able to infer that a structure on the chromosome tip that we now call the telomere protects the end of chromosomes from fusing with one another or with sites of DNA breakage[3]. Despite her research achievements and success in securing extramural funding, McClintock grew increasingly dissatisfied by her position at Missouri. In letters to Rhoades and Burnham in 1940, she expressed her frustration, feeling overworked and not adequately supported: "I have decided that I must look for another job. As far as I can make out, there is nothing more for me here."[4]

In 1941, McClintock accepted a research staff position in the Department of Genetics at the Carnegie Institution of Washington at Cold Spring Harbor, NY, USA. McClintock appreciated the intellectual freedom and independence she had at Cold Spring Harbor, where she remained active until her death in 1992. Working largely on her own, she enjoyed a very productive phase studying the peculiar instability of certain kernel mutants she had isolated genetically. This meticulous detective work would eventually lead to the identification of transposable elements. Through the 1940s, McClintock's scientific recognition continued to widen, resulting in her election to the National Academy of Sciences in 1944 and as President of the Genetics Society of America in 1945. Status and professional stability freed McClintock from the necessity of producing regular peer-reviewed publications in traditional journals. Most of her results leading to the discovery of transposable elements were reported annually in the Year Books of the Carnegie Institution of Washington.

Controlling elements

In 1948, McClintock reported "an interesting type of chromosomal behaviour"[5]. She observed that in a particular maize stock, chromosome 9 was recurrently breaking during kernel development at a locus she termed *Dissociation* (*Ds*), resulting in variegated pigmentation. Through a series of crosses, she could show that *Ds* breakage was controlled by the presence of another locus she called *Activator* (*Ac*). Strikingly, introducing *Ac* would lead to the mobilization (that is, the transposition) of *Ds* to another chromosomal location, while segregating *Ac* out would stabilize the chromosome. Furthermore, introducing *Ac* into other mutant stocks could destabilize previously stable mutations. Lastly, the *Ac* locus itself was capable of transposing to new chromosomal locations across generations. These surprising results were cemented by countless other experiments carefully recorded in McClintock's lab notebooks and summarized in the Carnegie Institution Year Books. A summary of her results on *Ac/Ds* was published in 1950 (ref. 6).

When McClintock first presented her astonishing findings on transposition at the annual Cold Spring Harbor Symposium in 1951, the results were largely met with bewilderment and scepticism. Some were convinced scientifically but argued that DNA transposition was an anecdotal oddity of maize. McClintock had a radically different opinion. She believed that the phenomenon she had uncovered in maize was central to the development of plants and likely other organisms. She later termed *Ac* and *Ds* not transposable but 'controlling' elements for their ability to control the expression of genes. Disappointed by the community's initial reaction, but undeterred, McClintock pursued the study of *Ac/Ds* and of a distinct maize transposition system she called *Suppressor–Mutator* (*Spm*). The *Spm* system had many similarities to *Ac/Ds*, including the separation of elements capable of mobility on their own, called autonomous, from those that necessitate the presence of another autonomous locus to transpose, called nonautonomous. But *Spm* had more complex properties that deeply intrigued McClintock. Remarkably, certain nonautonomous *Spm* elements would respond to the introduction of an autonomous element by modulating the activity of adjacent genes without even being mobilized. On the basis of these properties, she inferred that the autonomous element could generate a product with trans-regulatory activity — very much like the factors later shown to control gene expression in bacteria and subsequently in eukaryotes, which we now recognize as transcription factors. In 1956, she wrote: "Controlling elements are normal components of the chromosome complement and they are responsible for controlling, differentially, the time and type of activity of individual genes."[7] Hence, McClintock firmly believed that she had discovered a fundamental mechanism regulating gene expression.

This belief was fortified a few years later when François Jacob and Jacques Monod unravelled how the lactose operon of *Escherichia coli* is controlled. McClintock immediately drew parallels between the gene regulatory mechanism deduced by Jacob and Monod in the bacterium and what she had observed in maize with *Ac/Ds* and *Spm*[8]. By and large, the emerging molecular biology community ignored these parallels. The gap between McClintock and the genetics establishment grew wider as she continued to dissect the idiosyncrasies of *Spm*. Notably, her description of a *Spm* locus undergoing reversible and inheritable activation may be one of the earliest accounts of epigenetic regulation as we understand it now. Molecular work some 30 years later would reveal that *Spm* activation and repression correlate with reversible DNA methylation of the element. As groundbreaking as McClintock's research continued to be through the 1960s, she progressively retracted from the scene, increasingly refractory to communicating her results through publications and lectures. Yet, those who had the chance to interact informally with McClintock during those and

subsequent years have been uniformly marked by her infallible logic, far-reaching vision and brisk sense of humour.

Transitioning views of transposable elements

McClintock officially retired from the Carnegie Institution in 1967 but remained active in research and training at Cold Spring Harbor Laboratory as scientist emeritus. In the 1970s, McClintock focused on other aspects of maize genetics, including the crop's domestication and early spread through Latin America. Meanwhile, molecular biology was blossoming. It was now possible to isolate, manipulate and decipher the actual nucleic acid sequences that made up genes. In part owing to their abundance, transposable elements were among the very first DNA sequences to be isolated and sequenced. In bacteria, insertion sequences with properties reminiscent of McClintock's elements were discovered and implicated in the acquisition of antibiotic resistance. Like McClintock's elements, the bacterial transposons could excise out of the chromosome and reintegrate elsewhere directly as DNA molecules, defining what are now called class 2 or 'cut-and-paste' DNA transposons. Work in yeast, *Drosophila* and humans would soon reveal another class of mobile element that transpose via reverse transcription of their RNA into a DNA copy before being chromosomally integrated. These so-called retrotransposons or class 1 elements were found to be the most abundant in the human genome. By the early 1980s, it became clear that transposable elements are widespread across the tree of life, and transposition was recognized as a major mutagenic force shaping genomes. This realization triggered a series of prestigious awards to McClintock, culminating in the Nobel Prize in 1983 (Fig. 1). Transposons were finally mainstream. Or almost.

The next two decades were dominated by studies illustrating the mutagenic activity of transposable elements. The molecular characterization of mutations isolated in model organisms, including emblematic ones such as Mendel's wrinkled peas, Morgan's white-eyed flies or Lewis's homeotic mutants, would uncover how transposable element insertions and rearrangements can disrupt gene function in myriad ways. The identification of the P element as the root of hybrid dysgenesis in *Drosophila* revealed how uncontrolled activity of a single transposon can have catastrophic consequences on the fitness of an organism. Transposable element insertions were also found to cause disease in humans. All these findings jibed well with the concept that emerged in the early 1980s of transposable elements as parasitic, selfish genetic elements[9,10].

In 1980, Doolittle and Sapienza wrote: "When a given DNA, or class of DNAs, of unproven phenotypic function can be shown to have evolved a strategy (such as transposition) which ensures its genomic survival, then no other explanation for its existence is necessary. The search for other explanations may prove, if not intellectually sterile, ultimately futile."[10] According to this theory, the evolutionary success of transposable elements is not attributed to a specific cellular function, as McClintock envisioned, but simply to their ability to replicate independently of the rest of the genome, thereby ensuring their propagation without benefitting the organism, but sometimes at its expense — much like viruses. The kinship between transposable elements and viruses would receive support from the molecular characterization of retroviruses and retrotransposons, revealing striking similarities in their genetic organization and replication mechanisms.

The parasitic and selfish DNA concepts remain useful today and still provide the best explanation for the vast heterogeneity in transposable element content observed across species and even sometimes within species. However, it is possible that such categorization marginalized the study of transposable elements, dissuading scientists (or funding agencies) from testing McClintock's view of transposable elements as functional components of the genome. Although transposable element studies continued to flourish through the golden age of molecular biology, they primarily focused on dissecting the mechanisms by which they are mobilized and create mutations.

The shift from genetics to genomics at the turn of the millennium would trigger a seismic change in the perception and study of transposable elements. Large-scale genome sequencing confirmed that eukaryotic genomes, including half of the human genome, were filled with transposable element sequences. However, most transposable elements clearly looked like fossils, their coding sequences eroded with mutations, rendering them incapable of transposition. Genomes appeared like graveyards of transposable elements at various stages of mutational decay; the bigger the genome, the larger the graveyard. These findings lent credence to prior suspicions that a sizeable portion of the genome is devoted to doing nothing at all. It is 'junk DNA': sequences devoid of obvious cellular function. Transposition seemed the major source of this expendable material.

The ability to align large stretches of genome sequence from distantly related mammalian species such as human, mouse and dog enabled the origin and evolution of ancestral transposable element sequences to be traced. These analyses revealed that, once integrated into the genome, transposable element sequences generally accumulate mutations at the neutral rate of the species, showing no evidence of functional constraint — in stark contrast to sequences encoding cellular proteins. Of course, the same approach would reveal

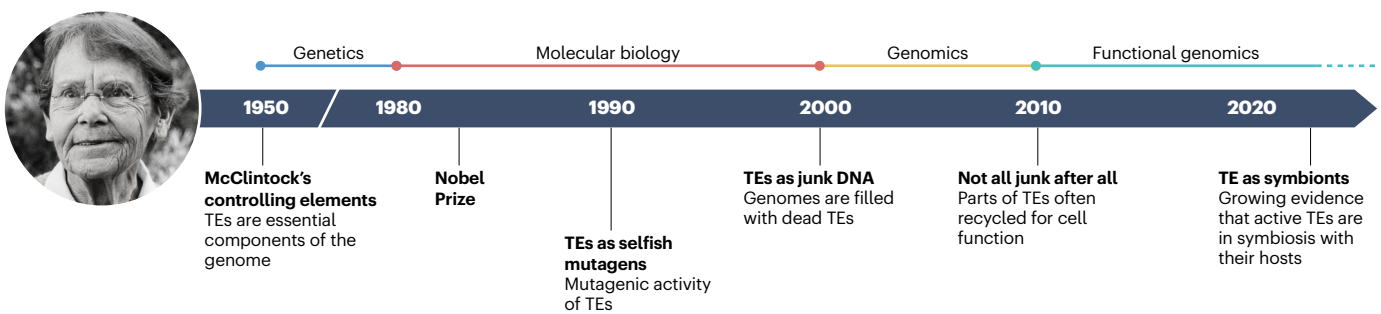

Fig. 1 | A timeline of paradigm shifts. Barbara McClintock's discovery of transposable elements (TEs) had a profound impact on our understanding of genome function and evolution and led to her being awarded the Nobel Prize in Physiology or Medicine In 1983. Barbara McClintock photograph credit: Science History Images/Alamy Stock Photo.

exceptional instances of transposable element sequences, both coding and non-coding, that have evolved under constraint, indicative of co-option for organismal function. Most, but not all, was junk.

The characterization of transposable element sequences repurposed for cellular function gained momentum with the advent of functional genomics. A battery of assays made use of high-throughput DNA sequencing to interrogate the biochemical activity of the genome in an increasingly comprehensive and unbiased fashion, including its precise transcription, the binding of regulatory proteins and the accessibility of chromatin. These studies revealed that transposable elements made greater-than-expected contributions to the transcriptome and regulatory apparatus of the genome, often with exquisite tissue or developmental specificity. Although these findings did not imply that all transcribed or regulatorily active transposable elements are functionally consequential, they overturned the idea that transposable elements are systematically silent and biochemically inert. Instead, a picture emerged of a genome in which transposable elements are dynamically responsive constituents — harking back to McClintock's later 'genomic shock' theory, which postulated that transposable elements enable organisms to remodel their genome in times of stress[11].

Transposable elements today

Today, we are better positioned than ever before to rigorously test McClintock's visionary hypotheses. Continuous advances in mapping and manipulating the genome, such as CRISPR-based technologies, have provided increasingly precise and powerful tools to dissect the functional impact of transposable elements. Recent research is depicting a more complex and nuanced view of transposable elements as diverse, sophisticated entities engaged in a continuum of interactions with their hosts, ranging from harmful to symbiotic. The activities of transposable elements are no longer perceived as peripheral or merely competing with cellular functions, but as deeply integrated into the physiology, development and evolution of species. Controlling and controlled, the elements are intertwined with virtually every facet of biology.

McClintock remains the only woman to be awarded an unshared Nobel Prize in Physiology or Medicine. Her struggles to find a fitting environment and a sense of belonging within academia have resonated across multiple generations. Her passion and perseverance in the face of scepticism, and her 'feeling for the organism' have inspired broadly. More than ever, Barbara McClintock is an iconic role model that we must continue to cherish and celebrate in our laboratories, classrooms and communities.

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Competing interests

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