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Mobile self-splicing introns and inteins as environmental sensors

Marlene Belfort

Self-splicing introns and inteins are often mobile at the level of the genome. Although these RNA and protein elements, respectively, are generally considered to be selfish parasites, group I and group II introns and inteins can be triggered by environmental cues to splice and/or to mobilize. These cues include stressors such as oxidizing agents, reactive oxygen and nitrogen species, starvation, temperature, osmolarity and DNA damage. Their sensitivity to these stimuli leads to a carefully choreographed dance between the mobile element and its host that is in tune with the cellular environment. This responsiveness to a changing milieu provides strong evidence that these diverse, self-splicing mobile elements have adapted to react to prevailing conditions, to the potential advantage of both the element and its host.

Address
Department of Biological Sciences and RNA Institute, University at Albany, Life Sciences Research Building 2061, 1400 Washington Avenue, Albany, NY 12222, USA

Corresponding author: Belfort, Marlene (mbelfort@albany.edu)

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Introduction

In the 1980s, with the discovery of mobile self-splicing introns in T4 bacteriophage, we conjectured that these selfish elements might play a regulatory role in gene expression [1,2]. We posited that these group I introns, which interrupt genes in a common pathway of nucleotide metabolizing enzymes, have the ability to act as sensors. Could introns be responsive to cellular and environmental cues, in ways that may be advantageous to their hosts? Little did we know then that the search for direct evidence would follow such a long and winding road.

Self-splicing mobile introns and inteins are usually bipartite, composed of both the catalytic splicing apparatus and a protein required for mobility. An RNA ribozyme is the splicing catalyst of group I and group II introns, whereas a protein enzyme comprises the self-splicing intein (Figure 1a). Group I introns and inteins use their associated homing endonucleases (HEs) to cleave DNA at precise targets and mobilize by homing through a double-strand-break mediated pathway (Figure 1a,b) [3,4,5•]. In contrast, group II introns move by an RNA-based retrohoming pathway. The excised intron reverse splices into DNA, in site-specific fashion, guided by base-pairings between the intron and the DNA. The integrated intron is then copied by the intron-associated reverse transcriptase (RT) (Figure 1a,c). A primer for the RT is provided by a nick into dsDNA introduced by HE activity associated with the RT. Alternatively, if integration is into ssDNA, such as at a replication fork, fragments of the lagging DNA strand act as primers (Figure 1c), resulting in target primed reverse transcription (TPRT) [3,6,7,8•,9,10]. Group II introns have also been shown to mobilize less specifically and at low frequency to ectopic sites, usually by the ssDNA pathway, a process known as retrotransposition. There is mounting evidence that all of these mobile self-splicing elements excise in a condition-dependent manner in response to a battery of signals, whereas the introns in particular also mobilize in reaction to various cellular stressors. The emerging picture is one of domestication, and that many of these invasive parasitic elements evolved opportunistically in concert with the host, mostly in both of their best interests.

Environmental triggers regulate group I intron self-splicing and mobility

Group I introns can have their splicing rate stimulated or inhibited, or their splicing pathways regulated by different environmental cues (Figure 1a). There are instances of chloroplast group I intron splicing being triggered by light, which is precisely the condition that requires the host gene product [11]. The mechanism of light-induced pre-RNA processing is unclear, but stimulation is affected by photosynthetic electron transport, which may impact the redox status of a protein that facilitates splicing. In contrast, there are several examples of bacterial and organellar group I introns that have splicing inhibited by a range of conditions. Inhibitory factors include small molecules, such as flavin mononucleotide (FMN) [12]. FMN acts as a competitive inhibitor of splicing by interfering with the affinity of the intron for GTP, which is the initiating nucleophile for group I intron catalysis.

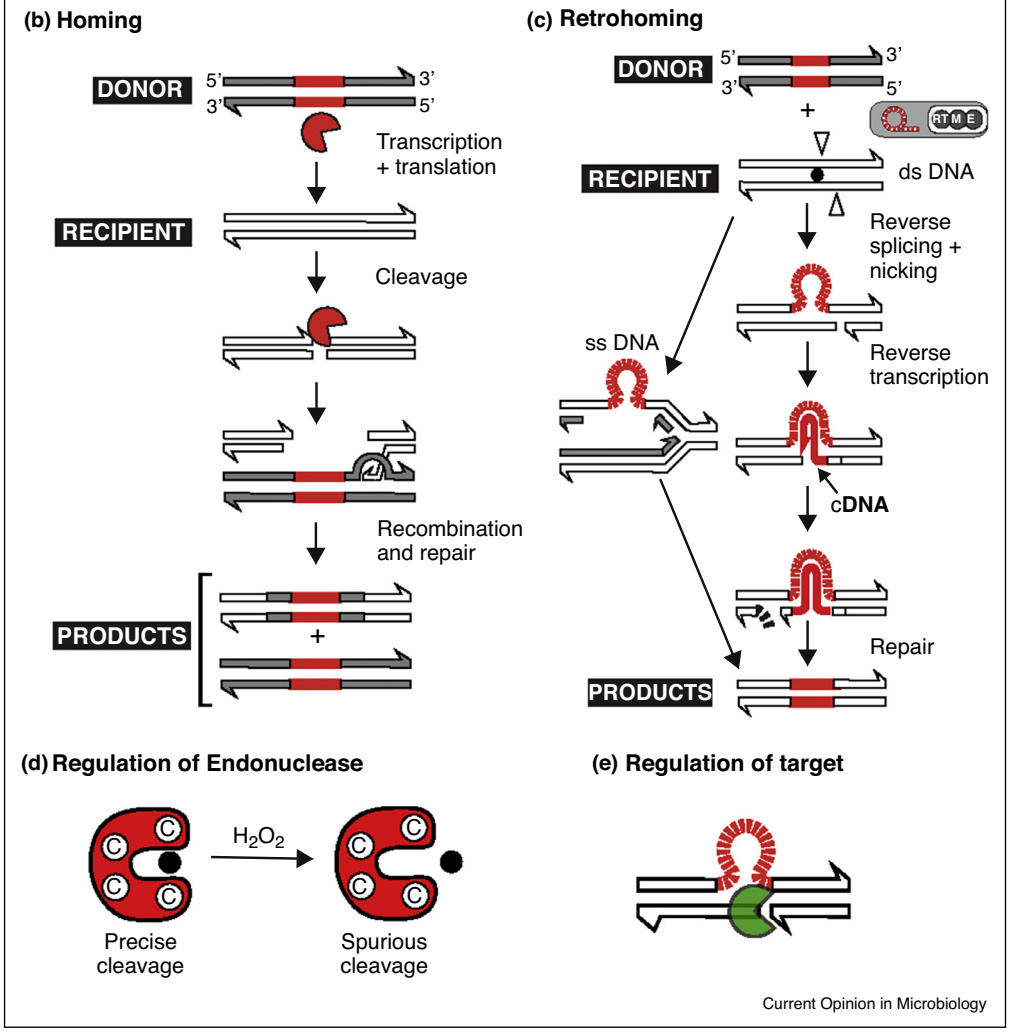
For T4 introns, growth state is important and stationary phase inhibits splicing [13]. This observation may be related to protein synthesis, where the act of translation

Figure 1

(a) Mobile self-splicing elements

Element	Self-splicing element	Pathway	Mediator	Splicing regulators	Mobility regulators
Group I intron	RNA	Homing (DNA)	HE[a]	Light,Redox FMN,Growth phase,Translation c-di-GMP	Oxidative stress
Group II intron	RNA	Retrohoming (RNA)	RT[b]-HE	pH Temp	Mg^{2+} Starvation Conjugation
Intein	Protein	Homing (DNA)	HE	ROS/RNS Redox, Temp pH, Salt DNA damage	None known

[a]HE = homing endonuclease
[b]RT = homing endonuclease



Mobile self-splicing elements.
(a) Overview of self-splicing, mobility and regulation. **(b)** Group I intron and intein homing pathway. The pathway is initiated by a HE encoded by the element (red Pacman symbol). After cleavage of the recipient the element is inherited by double-strand break repair recombination [42].
(c) Group II intron retrohoming. The pathway is initiated by reverse splicing of the excised intron into dsDNA followed by nicking of the opposite strand by the intron-encoded HE [7,8•]. Reverse splicing can also occur into ssDNA at replication forks (left). The ssDNA pathway is most