Why Prokaryotes Genomes Lack Genes with Introns Processed by Spliceosomes?

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Received: 26 September 2018 / Accepted: 26 October 2018 / Published online: 31 October 2018
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Until 1977, we thought that eukaryotic genes were like those of prokaryotes, that is, continuous sequences beginning with an initiation codon (ATG), followed by an open reading frame, always multiple of three bases (codons), and the message (mRNA) stopped when a stop codon (TAA, TAG or TGA) was reached. This paradigm, which historically seemed completely logical, changed dramatically when two groups, leaded by Sharp and Roberts (Berget et al. 1977; Chow et al. 1977), discovered that (at least some) eukaryotic protein coding genes were interrupted by non-coding sequences and eliminated from the mature (translated) mRNA before translation. Then, Gilbert (1978) coined the concept of *exons* (regions of the coding DNA that remained in the mRNA) and *introns* (the regions that are eliminated from the mature mRNA, and therefore are not present in the encoded proteins).

Today, there are no doubts that this discovery was a revolution in genetics. It not only challenged our previous definition of what a “gene” is, but led to discoveries and concepts such as splicing (that is, how introns are eliminated and exons are put together to make the mature mRNA), alternative splicing (how different exons from the same “gene” can be combined to make different proteins), or to the great discovery that some RNAs, once transcribed, can eliminate by themselves introns, a mechanism known as autosplicing (see, for instance, Bass and Cech 1986; Cech and Bass 1986; Guerrier-Takada and Altman 1986). In turn, the discovery of autosplicing not only reinforced the idea of the “RNA world” (for a review see Lehman 2015) but eliminated, forever, the time unanimous idea that proteins were the only catalytic molecules.

Therefore, the presence of introns in the majority of eukaryotic genes has challenged most of our concepts about genes, their regulation, their evolution, what is an enzyme... and last, but not least, why there are only probably fewer than 20,000 genes in the human genome while a “simple” organism like *Escherichia coli* has only around 4000. In other words, introns and how they are eliminated from the mature mRNAs has changed our concepts about molecular biology and evolution.

But given what we have said in the above lines (which of course do not pretend to be a review about the subject), there is a problem that, in our opinion, deserves some attention. As known, prokaryotes display an enormous divergence and different metabolic routes and lifestyles and occupy all known environments. Then, why did they never develop introns processed by spliceosomes? In the next few lines we shall propose an explanation.

Of course, the simplest one is that given that in prokaryotes transcription and translation are coupled, such a system should be a disadvantage from an evolutionary point of view. Furthermore, introns should be present. But there is no evidence that this was the case. Until now, nothing new. But there is a point that, in our opinion, seems very important.

As is known, the modern spliceosome, in its simplest form, is a complex of not less than ten different proteins and several RNAs. Let us imagine that this complex, or one even simplest, evolved in a prokaryote. And for some reason, which might be due to combine different genes in new, longest ones, it became fixed (or the existence or primitive introns). It is difficult to imagine such scenario, but let assume that it indeed happened, for example, “putting together” different pieces of genes from the same operon. This could be an advantage, because different pieces from different mRNAs could combine to produce new proteins with different, but related, functions. There is no biological constraint that can prevent this. Even more, it should be a new way to create new genes and, as a consequence, new functions. We stress that this scenario is hard to imagine just

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because (as far as we know) it did not happen. But if there was an example, it should not be a big surprise.

However in our opinion it did not happen because of another reason: one of the main forces in the evolution of prokaryotes is horizontal gene transfer (see, for example, Puigbò et al. 2010). As is known, for a gene (or group of genes) to be fixed several biochemical and evolutionary “steps” must be fulfilled, among them are: (a) to be transferred as a unit, (b) to carry (or to be integrated near) a promoter, (c) to not disturb the normal functions of the receptor, and (d) to confer a selective advantage.

Very probably, a putative “primitive spliceosome” (PS) was not as complex as the modern one. But in any case, it should be a rather complex particle, composed by several proteins and RNAs. For it to be transferred successfully, several conditions are needed: (a) All the components of the PS should be transferred simultaneously, which is hard to imagine, because we need to postulate a large “PS operon”, which probably did not exist as such, and therefore, multiple events need to be invoked, which is very unlikely. (b) Introns cannot be possible in the receptor (otherwise, it should have a PS), and if they did not exist, a PS machinery very probably should be extremely harmful for the receptor and eliminated from the population, because of the non-adaptation of genes to the action of the xeno-PS. (c) Even if a and b were disregarded (which of course is more than unlikely), new genes acquired by HGT by the receptor of PS should be negatively affected by the PS acquired. Hence, new events of HGT should be eliminated by the receptor, eliminating, as a consequence, one of the major forces in evolution.

Hence, we conclude that in the same manner that HGT was one of the main factors that contributed to fix the

universal genetic code; as postulated by Vetsigian et al. (2006), it could be a major force inhibiting the appearance (and fixation) of introns processed by spliceosomes among prokaryotes.

Acknowledgements Both authors are members of the Sistema Nacional de Investigadores, Uruguay.

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