Letter to the Editor

Present and future of ribonucleic acid interference

Presente y futuro de la interferencia por ácido ribonucleico

Dear Sir,

I would like to congratulate Dr. Pinazo-Durán et al. for the excellent editorial emphasizing a new phase in ophthalmology with a promising future, i.e., a highly active molecular biology field such as the genetic inhibition or interference with RNA (iRNA). The comments below are intended as a contribution to said editorial.

The Human Genome Project was an international initiative which between 1990 and 2005 disseminated the precise instructions defining living organisms, i.e., the full genome comprising 28,000 genes.

Recently, an international team of researchers has reduced the amount of human genomes to 19,000, thus requiring a redefinition of the genome mapping. However, the human body comprises between 50,000 and 100,000 different proteins, so obviously the numbers don’t work out. The concept of “one gene, one protein” belongs to the rigid Mendelian genetics. Until a few years ago, this concept was one of the cornerstones of genetics, but greater knowledge about DNA transcription and translation processes have done away with the idea that was one of the main dogmas of modern genetics. This is yet another example that proves that dogma should not exist in science. For instance, VEGF comprises several proteins which are the result of alternative RNA splicing of a single gene with 8 exons. And many more changes are yet to come.

The first project regarded as the inheritor of the Human Genome Project, the ENCYclopedia Of Dna Elements (ENCODE), has prompted some specialists to propose a new definition of genes: the union of genomic sequences encoding a consistent set of functional and potentially overlapping products. As the authors of said editorial point out, research with iRNA has advanced very quickly and new drugs have been developed. However, the disadvantages of RNA genetic inhibition are as follows:

1. Obviously, cells must have the ability of being transfected with the appropriate iRNA, although primary cells are difficult to transfact in comparison with cancer cell lines.
2. Even though iRNA exhibits disadvantages such as variability, non-specificity and incomplete inhibition, the main disadvantage of iRNA use must always be taken into account, i.e., the deviation effect (or off-target effect). Even though a high number of chemical modifications have been introduced to reduce the off-target effect of iRNA, it is necessary to continue developing more competent iRNA forms.
3. Unmodified iRNA is easily degraded by RNases, due to poor chemical stability and low mean life in circulation.
4. Transcriptions with large turnover are difficult to inhibit.
5. It is necessary to consider the induction of inflammatory immune response derived from the use of iRNA.
6. It is a very expensive therapy.
7. Sometimes it is difficult to fully understand the true endogenous function of in vivo molecules.

In fact, "we are in the midst of a crucial period of ophthalmological research based on RNA interference", but we must not forget that we are getting close to an essentially higher level of the therapy without resolving 3 unresolved issues in any iRNA system:

1. Off-target effect.
2. Appropriate administration system.
3. Induction of nonspecific immune response.

REFERENCES


* Please cite this article as: Asensio-Sánchez VM. Presente y futuro de la interferencia por ácido ribonucleico. Arch Soc Esp Oftalmol. 2015;90:554–555.


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