Possible Novel RNA-Mediated Transcriptional Activation Mechanism, called "RNA memory" Involved in Cell Identity

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None

Position-effect variegation (PEV) was discovered in Drosophila melanogaster in 1930 in a study of X-ray-induced chromosomal rearrangements. If a rearrangement places euchromatic genes adjacent to a region of centromeric heterochromatin, it gives a variegated phenotype that results from the random inactivation of genes by heterochromatin spreading from the breakpoint. After the establishment, the inactivation is henceforth clonally inherited. The vast majority of these modifiers were originally isolated in Drosophila as dominant mutations that suppressed or enhanced the variegation caused by a variegating white allele called white-mottled 4 (wm4). A large number of modifier genes alter PEV phenotypes. Genes isolated as PEV modifiers are usually of great biological relevance. The products of these genes are usually structural components of chromatin, enzymes that modify chromatin proteins, or are nuclear structural components.
The latest models of cell identity heritage explain best a "turn on - turn off" system of inheritable activation state of genes, via PcG or TrxG proteins or epigenetic modifications, but they lack an efficient way to explain how the fine quantitatively state of activation of each gene is inheritated. Even the classical model of PEV doesn't explain how, after the establishment, the activation state is quantitatively henceforth clonally inherited.

In my former research, we screened for white alleles that modify wm4 PEV. Our data showed that several hypomorph or null white alleles suppress PEV when in trans-combination with wm4. This effect is seen only when white alleles give transcripts; to suppress PEV and euchromatinize the variegating gene it is necessary the production of an RNA, even untranslatable, with sequence homology to the variegating gene. In my model, RNAs produced by white alleles act in trans to activate the transcriptional state of wm4 allele. I called this phenomenon "RNA memory" or "RNAmem".

I propose a model to explain this phenomenon. Through an unknown mechanism, after cell division, the transcriptional pattern of daughter cells is restored corresponding to the one of the mother cell, through the reading of some RNA fragments. Those RNAs are functional remnants of mRNA, which reflect the transcriptional pattern of the mother cell. The phenomenon is not a classical PEV suppression. It is a different biological phenomenon. It depends from sequence homology between the allele PEV suppressor and the allele whose PEV is suppressed.

In my model, the abundance of white messenger, even if produced by null or hypomorph alleles in a different cytological location, are able to activate in trans the wm4 transcription and to euchromatinize it.

There are some experimental evidence which could suggest a similar mechanism. In Drosophila, when PARP gene expression is impaired, the expression of PARP-e, an alternative splicing form for PARP which lacks its enzymatic activity, can restore the presence and the activity of PARP (Tulin A, Stewarrt D, Spradling AC: The Drosophila heterochromatic gene encoding poly(ADP-ribose) polymerase (PARP) is required to modulate chromatin structure during development. Genes Dev. 2002). In

culture cells NIH 3T3, a transfection for an inactive HO-1 raises mRNa and protein levels of wt HO-1 (Lin qs, Wells S, Yang G, Zhuang T, Abate A, Dennery PA: Catalytic inactive heme oxygenase-1 protein regulates its own expression in oxidative stress. Free Radic Biol Med. 2008).

I think we are in front of a basic biological phenomenon till now remained covered. RNAmem can be applied from pure research to applied biosciences, from cell reprogramming to the study of stemness, from the cure of cancer to the cure of human genetic diseases, and can drive a new biological revolution like RNA interference has done some years ago. Following my vision, RNA interference and RNA memory can be two biological phenomenon opposite and complementary.
Moreover, the possibility to combine RNA memory with RNA interference opens new incredible possibilities in understanding, changing, modulating and fine tuning the transcriptional state of cells.

If the model will be demonstate to be correct, the possible applications on human regenerative engineering are, of course, amazing.

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