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Editorial

CIENT PERIODIQUE

HMGA1-Pseudogenes: A Paradigm of Competitive Endogenous RNA Mechanism

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The genome of humans has been completely decrypted and, surprisingly, protein products are encoded by just 2% of our genes. Now, the leading goal of the scientific community is to unveil the dark matter inside the other 98% of the genome. Up to date, several studies underline that the mammalian genome gives rise to a great number of unidentified transcripts called "non coding RNA" (ncRNA), whose functions have not been entirely clarified. Among the ncRNA class, pseudogenes are usually defined as genetic relicts, since they lost their capability to produce functional proteins due to the acquisition of new genetic mutations. Indeed, they are nonfunctional relatives of ancestral functional genes missing their role throughout the evolution. However, a large body of data now underlines pseudogenes have key roles in both physiology and disease. Our research group has recently isolated two pseudogenes, *HMGA1P6* and *HMGA1P7*, both generated by an ancestral retrotrasposition of their parental gene *HMGA1*, a greatly involved-cancer gene. *HMGA1*-pseudogenes have just few mismatches in their mRNAs compared to *HMGA1* one. Consequently, they have almost the same microRNA Responsive Elements, so they are regulated by the same *HMGA1*-targeting microRNAs. In this scenario, the upregulation of *HMGA1*-pseudogenes can derepress *HMGA1* and others microRNA-sharing transcripts from the inhibitory pressure of microRNAs, giving rise to the so-called competitive endogenous RNA (ceRNA) mechanism. As expected, *HMGA1*-pseudogenes were found upregulated in several human cancer types such as thyroid carcinoma, pituitary tumors, ovarian carcinoma,

breast carcinoma, larynx carcinoma and their upregulation is positively correlated with *HMGA1* levels and other cancer-related genes (*HMGA2, EZH2, VEGF, IGF2, H19, EGR1*) that share the same microRNAs repressing action. In this way, *HMGA1*-pseudogene upregulation activates an oncogenic ceRNA network, where transcripts can talk each other by competing for microRNAs. To deeper investigate the *HMGA1*-pseudogenes roles, we generated two transgenic mouse models: one for *HMGA1P7* and another for *HMGA1P6*. Interestingly, Mouse Embryonic Fibroblasts (MEFs) derived from *HMGA1*-pseudogene transgenic mice showed a higher growth rate and senescence later than the wild-type counterpart, confirming the oncogenic ceRNA crosstalk induced by *HMGA1*-pseudogene. In particular, preliminary results show that about 50% of *HMGA1*-pseudogene transgenic mice sacrificed at 18 months of age displayed a lymphoid pathology. In fact, the *HMGA1*-pseudogene transgenic mice spleens were characterized by a large increase in size (splenomegaly) and by a lymphoid hyperplasia. Intriguingly, preliminary observations suggest that these mouse models develop carcinomas in several organs such as kidney and liver. Altogether these data strongly support the hypothesis that ncRNAs may have causal role in carcinogenesis acting as ceRNA transcripts. In conclusion, this research topic will expand the theory of the ceRNA mechanism dynamics and complexity of the noncoding RNA regulatory network, providing more challenges in the development of new strategies for ceRNA-based cancer diagnosis and therapy. Indeed, the characterization of *HMGA1*-pseudogenes as novel biomarkers associated with tumor progression will provide an important impact on clinical practice leading to the development of a new tool for more precise prognosis or treatment of patients, especially those that respond poorly to medical therapy.