

# CHAPTER 1

## Gardener of miRNA in Oxford

### —microRNA Blossoms

The problem of self-delusion arises simply because science, like art, is an interpretative activity. Webster, S. *Thinking About Biology*

### Overview

Genetic trait is the curious issue for biological research to elucidate a cause of pathogenesis as well as its transmission from a cell to a cell, from individuals to individuals, and from species and species. Although it has been known that transmission of human genetic trait is only due to inheritance by DNA from a mother to children, its conceptual scheme has been broken. At the first, a genetic trait of human immunodeficiency virus (HIV)-transmitted humans has the retroelement (RE) including retrovirus and approximate 50% of the human genome is composed of the general REs. The microRNA (miRNA) gene is thought to be evolutionally born from the REs and it is a real story because of the presence of an HIV-1 miRNA. Further, the miRNA genes in the RE enveloped can move from one to another and similarly the miRNA own itself enveloped by a microvesicle should be transmitted via blood, cerebrospinal fluid, urine, feces, tears, salivary, ascites, sweat, semen and milk without enzymatic degradation. Maternal genetic trait could be inherited via

the miRNA genes in milk microvesicle to children, in turn vertically acquired characters should be transmitted with the miRNA genes to a descendant, previously called as environmental factors in Darwinism. Although it has not yet been established what is the environmental factor like the dark matter of the space, one of environmental factors is the food's miRNA gene and the foods' miRNAs in microvesicles could affect human health, simultaneously the foods' miRNA genes as well as protein coding and non-coding genes have linkage with genetic traits, sometimes evolutionarily by homing into the human genome by the REs. Therefore, the miRNA gene alteration has an important role for adaptation of humans to the environment and then the acquired information should be inherited with the miRNA genes from a mother to a descendant. Thus, the information gene is miRNA rather than DNA, so called as "RNA information gene (Rig)" because most of all diseases are caused by aberrant expression of Rigs. Further, the Rigs in microvesicles may travel from another planet to the earth and vice versa through the interstellar. Since diseases are the RNA gene disease, like that, evolution may variously run among species dependent upon Rig sets from the chaos to the cosmos, so called "programmed evolution". The RNA wave has just been the central dogma of life and is making an epoch in the history of social revolution to change our life style.

In this chapter, about curiosity of the microRNA information gene is described. Most of you already will know that we have been lived with microRNAs in our life. Again, I am a virologist, therefore, I will be endeavoring to explain about the relation between HIV-1 infection and microRNAs, and subsequent RNA wave 2000 to human healthcare in this book.

## 1.1. 1987 Oxford

Dr. Cookson [1994] described in his book, *Gene Hunter*, "Curiosity is a genetic trait shared by many species." HIV has a genetic trait, that the particle of HIV-1 has a single stranded RNA. If I make sense as a standard researcher of RNA, I would have thought that single stranded RNA is easy to be broken down by nucleases, therefore, the single stranded RNA has no function, that is a template of DNA for making

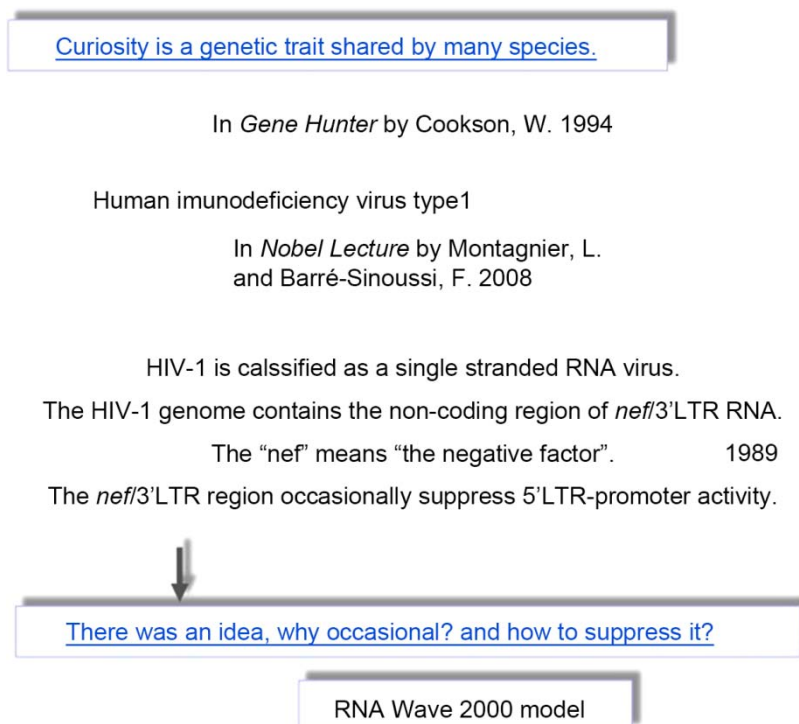
protein. But I am a virologist and probably mad. In early time, Drs. Cheng-Mayer and Niederman [1989] have been reported that a negative factor of HIV-1 replication was so named as *nef* because the *nef*/LTR can suppress viral transcription from LTR. However, using Nef protein, the mentioned *nef* activity has different outcomes, controversial Nef protein function has been documented as a positive factor. Further, the mechanisms of this down-regulation of transactivation are not completely clear. I thought why *nef*/LTR region occasionally suppresses in transcription of LTR-CAT reporter genes but at most of all time experimental results were failed in the same assay. Because there may be some factors that are not protein, not lipids, not sugar chain and not DNA. When I was 31 years old in the Institute of Virology of Oxford at UK since 1987 and was employed in Medical Research council (MRC) of Cambridge as a scientific officer, I had an idea that small RNA from *nef*/LTR region could affect the viral replication in a mild tone, suggesting RNA wave 2000 model (**Figure 1** and **Figure 4**). Because HIV gene recombinant baculovirus- infected insect cells made large amount of  $^{32}\text{P}$ -labelled small fragments in the gels; however, every researchers thought that most all low molecular weight bands are free  $^{32}\text{P}$  and the low position of developed X-ray film had been trimmed and trashed. Later, it has been reported that arbovirus RNA genome can make miRNA-like small RNAs [Asgari, 2014]. At previous time, therefore, and at first time, I had to show the concrete evidence that Nef protein is not implicated in the promoter interference and the Nef protein has another character alone, to show my basic idea that microRNA (miRNA) is transcriptional and translational suppressor.

HIV-1 RNA is reverse-transcribed and can be integrated into the human genome. Human papilloma virus has a double stranded circular DNA genome. Papilloma virus and HIV-1 have different nucleic acids genome. Papilloma virus is implicated in the development of epithelial malignancies, especially cancer of the uterine cervix. Papillomavirus E6 and E7 proteins inhibited tumor suppressor p53 and Rb proteins, which are well known explanation of carcinogenesis by infection of papillomavirus. Although different chemical core of both genomes have, HIV-1 infection also induces human malignancies. Further, HIV-1 did not have remarkable carcinogen protein. Each event suggested what is something new to understand the car-

cinogenesis, which was inspired by Dr. Zur Hausen's words [2008], and mentioned as "Research on infectious causes of human cancers has a great potential for future surprise." I thought that there are some universal substances in RNA and DNA viruses, which are small RNAs transcribed from viral genome and host genome, suggesting RNA wave 2000 (Figure 2).

## 1.2. 1983 Mobile RNA Element

Dr. McClintock [1983] presented that genetic element can jump from one to another position of a chromosome. She talked me in my dream that if the small



**Figure 1.** AIDS research work's curiosity in micro and nano. Human immunodeficiency virus type 1 (HIV-1) has two single stranded plus RNA genomes in a virion but they did not form helix structure and that are resistant to RNase. Further, HIV-1 RNA genome has noncoding region, called as LTR. The *nef* in the LTR showed negative activity against HIV-1 proliferation but it has not been cleared that what *nef* can work and how.

[The search for infectious causes of human cancer.](#)

In *Nobel Lecture* by zur Hausen, H. 2008

Human papillomavirus type 16 & 18



E6 and E7 inhibit tumor suppressor proteins p53 and pRb.

Research on infectious causes of human cancers has a great potential for future surprise.

HIV-1 infection also induces human cancer, such as Kaposi's sarcoma, Non-Hodgkin's lymphoma and primary central nervous system lymphoma.

[There was an idea, what is new to understand carcinogenesis?](#)

RNA Wave 2000

**Figure 2.** A sign from Montagnier and Barré-Sinoussi to zur Hausen. HIV-1 may not be a virus. It is just RNA information. HIV-1 can induce tumor like human papillomavirus (HPV), which is a DNA virus but HIV-1 has not carcinogenic protein such as E6 and E7 of HPV. Further, E6 and E7 proteins themselves did not show tumorigenic activity *in vitro*. From these evidences, oncogenic activity may be derived from small RNAs, miRNA it is it.

RNA jumps from the HIV-1 *nef*/LTR transcript from the human genome, the small RNA could control HIV-1 latency, negative reaction of HIV-1 replication as well as host homeostasis. Host small RNA may inhibit HIV-1 replication. Further, these small RNAs can move anywhere and induce carcinogenesis. I awoke to find myself elegant, I should add the new gene as a micro-RNA and nano-RNA to present biology, and escape from the dogmatic DNA world to imaginative RNA world. This is RNA Wave 2000 (**Figure 4**).

miRNA as a mobile genetic element induces transcriptional and post-transcriptional regulation of genes. miRNA expands to inter- and intra-cellular, and inter- and intra-organ, or inter-species and intra-species into the environment. Small