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Highlight

The odds of small things☆

Great things are done by a series of small things brought together. The internet at least does not lack for complaisant quotes and advice with a spiritual touch, ranging from Mother Teresa to Vincent Van Gogh. Usually they go hand in hand with nice photoshopped wallpapers of sunsets and cloverleaves.

Two decades ago, a funny tiny piece of RNA was discovered in the worm *Caenorhabditis elegans* [2] and for the rest of the millennium, no one really cared, despite those sage dicta. Sure, the *lin-4* gene encoded a 22 nucleotides-long RNA with no sign of translation into a protein and seemed to prevent the one of the heterochronic *lin-14* gene, in charge of developmental timing [3], but this was dismissed as a worm's caprice [4,5]. Neither the discovery of *let-7,* in 2000, [6] nor the initial discovery of RNA interference (RNAi) in 1998 by Andrew Fire and Craig Mello [7,8], still in *Caenorhabditis,* attracted much more attention, until it became clear in 2001 that those *microRNAs* are in fact a huge family of molecules and conserved from insects to mammals, thus humans [9,10].

The following boom of all types of small RNAs and RNAi quarried the Nobel prize of Medicine 2006 for Fire and Mello as well as more than 30 000 known mature microRNAs in 206 species up to date [11]. The human genome alone encodes over 1000 microRNAs, which are said to target about 60% of all protein-coding genes in a time and tissue-specific manner, as one microRNA has many targets and one target usually binds several different microRNAs, allowing thus for a dense network of interconnected control [11,12].

Hailed as *the* new paradigm of gene expression regulation of the past decade in virtually any cellular process [2], fueled by the latest advances in RNA sequencing techniques [13], microRNAs received the ultimate distinction when it became clear that their expression tended to be commonly deregulated in all types of pathologies, from cancer over cardiovascular diseases to metabolic disorders, launching a trend to collect the highest number of correlations between troubled microRNAs and troubled health [14]. Infection and immunity, strangely, were not among the top members of the list, despite the fact that RNAi is an essential part of the defense against unwanted nucleic acids, like transposons and viruses, in plants and invertebrates [2,10]. Although, it seems only natural that the merciless hide-and-seek game between pathogen and host, where no holds are barred, won't shy away from using the small caliber. Indeed, since a few years, the regulation of microRNA expression is increasingly recognized as an essential component of both the host response and the pathogens' strategies to hijack host cell pathways [12,13].

Of all pathogens, viruses maintain the most intimate molecular relationship with their host. Stripped from their protein coat, their respective genomes share one cell, entangle and may even fuse. As an unavoidable consequence, their main battlefield is genomic regulation. What follows should provide enough scenario ideas for a year of television series, an evolutionary tale full of action, coalitions and betrayal, embezzlement and theft, just like a thousand times enlarged insects make great science-fiction monsters. Let's have a look at the utterly complicated script...

As mentioned above, eukaryotic host cells are full of microRNAs, and part of them are specifically in charge of antiviral activities [2]. The most direct strike of some, often upon activation by the interferon pathway, is to directly attack the viral RNA, targeting it for destruction or blocking its replication [2,12,14,15]. This being not enough, they frequently practice the scorched earth policy, repressing cellular factors that risk to make life too comfortable for the invader [2] – miR-223 is obviously one of them – while taking care that inflammation does not spin out of control *via* negative feedback loops on its main actors [12,14,16].

And then, the virus strikes back. Some interfere with the host microRNA production machinery [12], others titer away the little aggressors [12,15], mask or shorten their binding sites [15,17], or evolved 3′ UTRs (untranslated regions) with complex secondary structures, restricting RISC binding [4,17].

Ironically, even if RNAi probably appeared as a defense against nasty genetic elements, such as viruses, the latter enthusiastically picked up the idea of small, polyvalent, non immunogenic tools for their own purposes [8,10]. One decade ago, the first viral microRNAs were discovered [14,18], nowadays over 250 are known mainly in DNA viruses, with the herpesvirus holding the quantitative record [10,13]. With the increasing reports of noncanonical cytoplasmic and Drosha-independent processing [2,4,11], evidence for RNA virus microRNAs is growing but still controversial [4,8,10]. In any case, viral microRNAs are quite straightforward and serve

☆ Article highlight based on "miR-223 inhibits dengue virus replication by negatively regulating the microtubule-destabilizing protein STMN1 in EAhy926 cells" by Na Wu et al. [1].

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their master's basic purposes – prolonging the longevity of the host cell, escaping the immune response and controlling the lytic cycle [10]. This in mind, they charge any dissenting host factor, from the interferon response to apoptotic genes [2], with from time to time some accidental secondary effects such as cancer, due to an excessive encouragement of preventing cell death, proliferation and avoiding the immune response. Having learnt some refinement from their hosts, viral microRNAs may also target their genome of origin, usually in order to lower the viral protein production and thus its antigenicity, and to favor latency [2,10].

Things got nasty when the virus started to hijack the host microRNAs for their own agenda, either stimulating or repressing their expression according to the desired effect [2]. HIV-1 (human immunodeficiency virus 1) apparently uses a cluster of cellular microRNAs enriched in resting CD4+ T cells to keep its protein production down to escape the immune system and quietly establish a viral reservoir [2,4,8]. But the most famous example comes from the Hepatitis C virus (HCV) and his affair with the cellular miR-122, highly abundant in liver [15]: the 5′UTR of the HCV genome lures two miR-122 molecules and Ago2 proteins to its seed sites and the resulting complex protects the viral RNA from degradation, promotes its stability and propagation and enhances translation [4,10,11,17].

Establishing a comprehensive catalog of all implicated microRNAs in the complex interplay between host and virus and labeling their roles as friend or foe, depending on the cell type, is an ongoing Herculean work.

To note, viruses are the most studied pathogens in terms of microRNA matters, but not the only ones able to traffic the cellular small RNAs. Bacterial LPS (lipopolysaccharides) quickly attract the attention of a large set of cellular, immune system-related microRNAs [13,14]. Bacteria in turn, excel in rerouting numerous host pathways for their purposes by injecting virulence factors in the host cytoplasm. MicroRNAs do not escape the rule and serve to suppress apoptosis and pro-inflammatory pathways, and to delay epithelial self-renewal. However, the bacterial effect on the host organism is not necessarily harmful. Gut microbiota recently moved into the limelight thanks to several studies showing their microRNA-mediated role in the establishment and maintenance of an appropriate intestinal mucosa homeostasis, barrier function, xenobiotic metabolism and low inflammatory environment as well as in the control of pathogenic bacteria [12–14]. Finally, host microRNA modulation was also observed upon infection with various parasites and fungi [14].

Without doubt, one can spend a long time marveling at the extraordinary complexity of the molecular chess between host cell and pathogen, but earlier or later, the nagging question of the concrete application shows up, usually in the last paragraph of any article. Therapeutic microRNA tools are admittedly still in their infancy. Certainly, specific microRNA profiles make good biomarkers and prognostic tools without major effort [2,12,15], but since they turned out to be active players in the pathogenesis process or the cellular defense system instead of simple passive bystanders, this option is not satisfying. Viruses hide among the civil population, the host genome, and harming the virus without harming the host is a delicate maneuver and the principal reason for the low number of effective antiviral drugs [2]. In theory, microRNA mimics or antimiR oligonucleotides hold the promise of nontoxic antiviral therapies with little risk of resistance emergence [1,11]. In praxis, safely getting the molecules at the right dosage into the right type of cells of the organism is far from being trivial. There are a few concrete attempts, though. Mima Therapeutics started a phase 1 study, giving a liposome-formulated miR-34 mimic based drug to patients with primary liver cancer, while Santaris Pharma successfully passed its antimiR Miravirsen, directed against the notorious miR-122, through a phase 2 study in HCV patients, proving long-lasting antiviral activity, thus greatly fueling this area of research [4,11]. If this works only for a few exceptional candidates or on a larger scale, is yet to find out.

In the meantime, who will be next on the list of new actors in the screenplay of infection? Long noncoding RNAs, the latest darling of molecular geneticists, hold great potential to get the leading part, potentially by regulating in turn the cellular or pathogenic microRNAs [2,10,14,15].

And how does *Be faithful in your noncoding RNA, it is in them that your fine-tuning lies* sound? I could imagine a nice wallpaper filled with RNA loops...

1. Biosketch – Jing An

Jing An got her Masters degree and PhD in Clinical Medicine in 1989 at the Third Military Medical University in Chongqing of China, followed by a postdoctoral position and research fellow position at the Department of Microbiology and Immunology in Tokyo (Japan) at the Metropolitan Institute for Neuroscience. In autumn 2000, she returned to China and occupies since the position of a principal investigator and head of the Department of Microbiology at the Capital Medical University of Beijing (China). Dr. An's research focuses on the interaction between dengue and host as well as on prevention of dengue virus infection.

2. Interview with Jing An

1. *What triggered your interest in the link between dengue infection and host microRNAs?*

Dengue virus (DENV) is the etiologic agent of dengue fever (DF), which has been the most common mosquito-borne infection in tropical and sub-tropical regions of the world. The incidence of DENV infection has increased 30-fold over the last 50 years. In 2013, the annual global incidence estimated