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Editorial: Host response to veterinary infectious diseases: role of coding and non-coding RNAs as biomarkers and disease modulators

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Editorial on the Research Topic

[Host response to veterinary infectious diseases: role of coding and non-coding RNAs as biomarkers and disease modulators](#)

Introduction

The motivation behind hosting and maintaining this Research Topic is the interest in the roles of host non-coding RNAs in infectious and zoonotic diseases, which we believe is underappreciated in veterinary medicine, at least relatively to its counterpart in humans. The latter is fueled by the evolving role of these molecules in human cancer research (1). The aim of this topic is not only to draw scientific attention to the involvement of coding RNAs (i.e., mRNAs) in veterinary infectious diseases but also to portray their intricate relations with non-coding RNAs (sncRNAs), which feature multiple species such as microRNAs (miRNAs), small nuclear RNAs (snRNAs), small nucleolar RNAs (snoRNAs), and Piwi-interacting RNAs (piRNAs), in addition to long non-coding RNAs (lncRNAs). Aspects such as their regulation in animal infection with various pathogens, their biomarker potential, and their biogenesis were and will continue to be covered here. After almost 2 years of publishing this topic within the remit of *Frontiers in Veterinary Sciences*, we are continuing at a steady and successful pace to attain our anticipated impact. With six articles being published, the topic has witnessed a big leap in article views, from 2,354 views at its launch in 2021 to around 13,000 views in July 2023. These numbers, along with other statistics shown on the topic website, already mirror the uniqueness of this field and calls for further in-depth exploration.

RNAs in veterinary infectious diseases: where we are: reflections from published articles in the topic

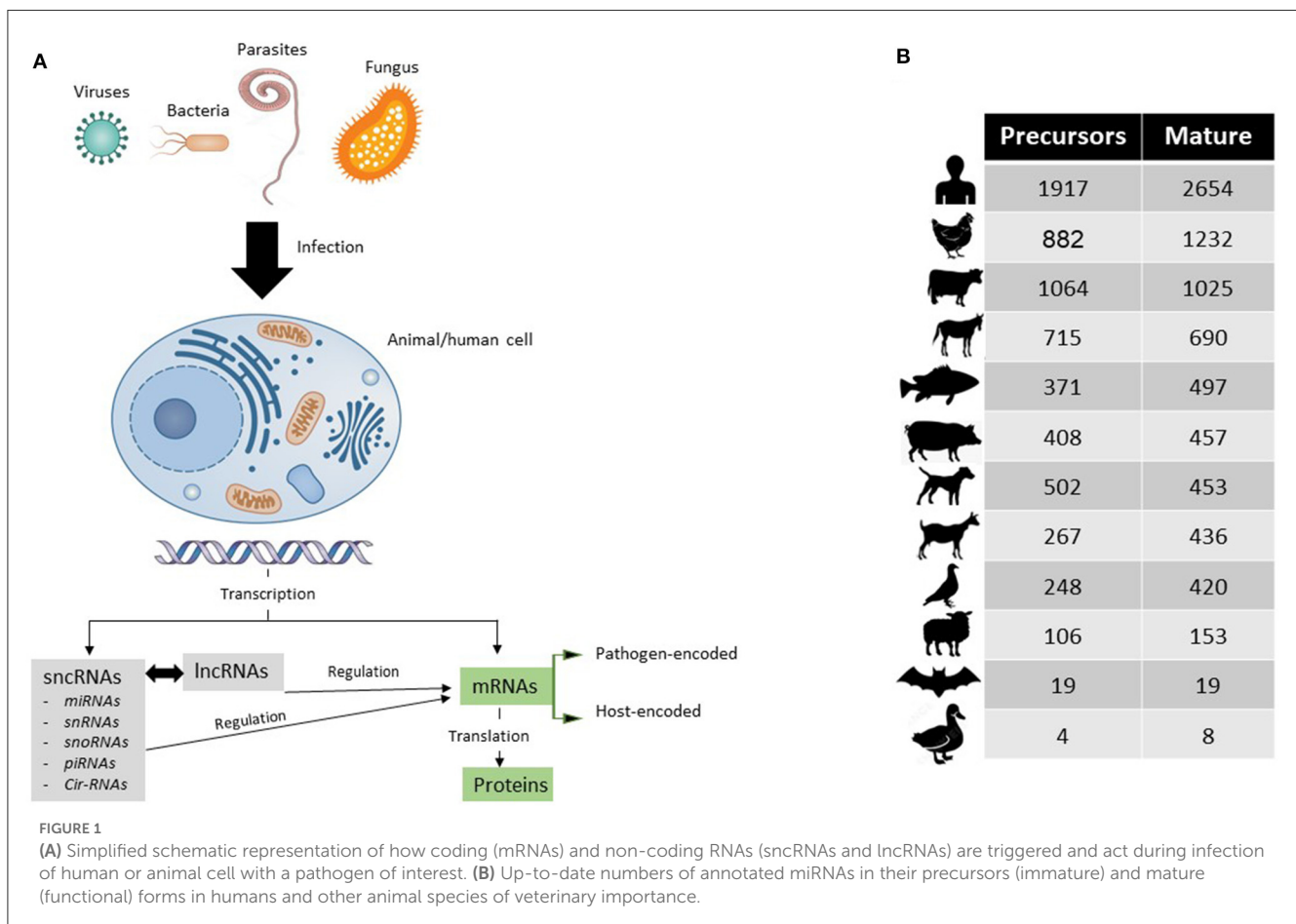
Around 80% of the genomic DNA is transcribed, leaving out 20% as the non-transcribed portion, the so-called junk DNA (2). Only 1–2% of the transcribed mRNAs are translated to protein, and the remaining 78% encompasses ncRNAs that can be either small sncRNAs (<200 nts) or long lncRNAs (>200 nts) (3). These ncRNAs regulate the functionality of other mRNAs (Figure 1A).

Studies on mRNAs have been exploring wide aspects of the pathobiology of significant viruses such as avian influenza viruses in chickens (4, 5) and bovine viral diarrhoea in bovines (6), zoonotic parasites such as toxoplasma (7) and cryptosporidium (8), and economically important pathogens that cause mastitis in bovines or caprine (9, 10). In virtue of small RNA sequencing, similar studies are being conducted at a limited scale on miRNAs and other sncRNAs. Both sncRNAs and lncRNAs could fine tune gene expression at the transcriptional stage and posttranscription (11). Since the discovery of the first microRNAs (miRNAs), named as *lin4*, in 1993 by Lee et al. in *C. elegans* (12), an obvious growth of miRNA numbers has been evidenced. By now, 38,589 miRNAs have been annotated in the most recent version of miRbase (release 22.1) (13). Figure 1B shows the most recent numbers of annotated miRNAs in the miRbase database.

It is not surprising that mastitis, a tricky problem in dairy farming that causes decline of milk quality and remarkable economic losses (14), has become an active area of research for sncRNAs. The signature and potential function of lncRNA associated with *Staphylococcus aureus*-caused mastitis in bovines have been explored in some studies (15). Comparable efforts were conducted for miRNAs in the same context (16, 17). An article in our Research Topic (Luoreng et al.) tried to tackle this problem and highlighted the roles of upregulated miRNAs (miR-320a, miR-19a, and miR-19b) and other downregulated ones (miR-143, miR-205,

and miR-24) as diagnostic markers for *Staphylococcus aureus*-caused mastitis at the 5th and 7th day in an experimentally infected animals. MiRNA regulatory functions have been also revealed in a plethora of infectious diseases affecting animals [comprehensive reviews are available here (18–20)].

Given the epigenomic regulatory role of sncRNAs on mRNA genes, a common approach is to dually investigate the changes in sncRNAs and their target mRNAs. This would provide a holistic picture of what is operating during an infection event (21). A study published in our topic by Chen Q. et al. exemplifies this trend in canine distemper virus infection in an understudied host, the mink. The authors found that mir-140-5p and mir-378-12 targeted corresponding mRNA genes in the NF-kappa B signaling pathway. The JAK-STAT signaling pathway was found to be regulated by mir-425-2, mir-139-4, mir-140-6, mir-145-3, mir-140-5p, and mir-204-2. Similar studies were also performed in the context of avian influenza infection, yet these focused on mRNA-lncRNAs interaction (22). Another research line has been the RNA interference (RNAi), a phenomenon that involves an interaction between natural or artificially introduced RNAs into the cell to physically bind a target mRNA, thus leading to gene silencing (23). The role of RNAi has just emerged in the veterinary infectious disease field. A plethora of studies have studied the consequence of this process on viruses (24–26) and parasites of veterinary importance (27, 28). As shown in one of the articles published in this topic, short hairpin RNA (shRNA), a form of RNAi, was found



to suppress the replication of border disease virus (Hajihassani Arani et al.). Border disease is a viral sickness of small ruminants and pigs (29) that might lead to symptoms such as infertility, abortion, stillbirth, and the birth of tiny, faint young (30).

Knowledge gap: aspects to be addressed in future research

Highlighted here are some knowledge gaps that still need to be addressed. With the expanding universe of sncRNAs (31), some of their species have remained superficially studied or have not been investigated at all in the context of animal infectious diseases. PiRNAs, snoRNAs, and circular RNAs (circRNAs) are examples of these overlooked molecules. Using a duck model for H5N1 influenza virus, we have identified an organ-specific expression pattern of piRNAs (32). Others have investigated roles of piRNAs in insects that could allow to combat insect-borne diseases (33). Interestingly, the genes involved in the piRNA pathway are more rapidly evolving compared with other RNAi genes. Our Research Topic is becoming a platform to explore some of these overlooked molecules. The article published by Chen L. et al. showed that circular RNAs interacting with miRNAs and mRNAs could shape the host response to Newcastle disease virus (NDV), a devastating chicken virus. They found that many circular RNAs were differentially regulated and can determine the NDV-induced metabolic changes in chicken embryo fibroblast cells via regulating mRNA and miRNAs. They identified that just one of these circular RNAs, circ-EZH2, inhibited NDV replication when overexpressed, indicating that circRNAs are involved in NDV replication. These studies and others call for additional research on this topic. An annotation database also needs to be continuously built, refined, and further completed for ncRNAs in less annotated animal species. Surprisingly enough, miRbase, the miRNA database, lacks annotation for miRNAs in cats, an important feline species. A broad yet valid question is to what the extent the epigenomic and regulatory logic of these sncRNAs is conserved across animals and how this contributes to zoonotic potential or a cross-species transmission of the pathogen. It is very important for researchers in this field to remember that *in vitro* models of infection (e.g.,

cell lines and organ cultures) are by no means a reflection of the mechanisms occurring in the respective natural animal hosts of the pathogens of interest. Similarly, the use of non-traditional animal models poses challenges of background genetic differences, rendering the model non-representative. Considering the economic deficits in middle- and low-income countries, which cast a shadow on the lack of funds given to researchers, it is recommended to keep the studies as complete as possible, even if conducted on a small scale, in a way that enables reaching solid conclusions.

Altogether, the field of coding and non-coding RNAs is rapidly evolving, and the roles of these molecules in the pathogenesis and outcome of veterinary infectious diseases are being continuously discovered. This Research Topic represents a platform to explore these aspects. The investigation of these molecules at the host level could lead to remarkable discoveries, from biomarkers for infection to therapeutic avenues, that researchers and veterinarians could use for combating veterinary infectious diseases.

Author contributions

MS: Conceptualization, Visualization, Writing—original draft.

Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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