

Signals During Sex: Could They Be in the RNA?

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In addition to enhancing fertility in a female partner, semen, which consists of sperm cells and seminal fluid, is believed to also exert an immunosuppressive effect. The assumed purpose is to protect the fertilizing sperm cells from recognition and attack by the immune system in the female genital tract. On the downside, this immunosuppression could contribute to the transmission of sexually transmitted diseases. It has been shown that the seminal plasma rather than the cellular fraction of semen is responsible for this immunosuppressive effect; however, it's unclear what mediates it exactly. Potential candidates include exosomes, secreted vesicles that have been shown to mediate intracellular communication in a variety of tissues. Researchers in the laboratory of Dr. Florian Hladik in the Vaccine and Infectious Disease Division carried out an in depth analysis of the nucleic acids contained in seminal exosomes (SE) to determine the possibility of regulatory signals being transmitted via these exosomes.

The researchers found that among other components, SE transported many small non-coding RNA molecules. Via isolation and sequencing of this RNA, the researchers identified several types of small RNA, including microRNA, ribosomal RNA (rRNA), transfer RNA (tRNA), Y RNA, and protein coding messenger RNA (mRNA) fragments, among others. The characteristics of these RNA sequences allowed for several conclusions to be drawn.

Postdoctoral fellow Lucia Vojtech, who was first author on the study, explained, "we were surprised to find a high prevalence of small non-coding RNAs that are not traditional microRNAs. These RNAs, including tRNA fragments and Y RNA, enriched in seminal exosomes in a way that was consistent between donors—so they could be functionally important." For example, the microRNA component included in SE represented only 175 out of the nearly 2600 known microRNA species, with ten of these making up >40% of all microRNAs present. microRNAs are small non-coding RNA molecules involved in epigenetic control of gene expression by interfering with specific gene transcripts prior to their translation into proteins. In addition to microRNA, SE carried other small regulatory RNA molecules.

Further analysis revealed a connection to immune regulation among the detected RNA sequences. Several of the most abundant microRNA species, including the top four, are known to regulate the translation of immunity-related proteins. Also, several specific tRNA fragments that are known to

inhibit protein translation non-specifically were detected. Thus, these molecules could dampen certain immune responses in the recipient female genital tract.

These findings highlight the importance of this research towards the broader objectives of disease prevention. Several HIV vaccine candidates have induced robust anti-HIV immunity in the bloodstream. Despite this, protection from HIV infection in the genital tract during sex has proven to be difficult. The immunosuppressive properties of semen could be partially to blame. By better understanding the mechanisms behind this effect, this research may lead to advances in the prevention of sexually transmitted diseases and vaccine development.

"Moving forward, we are excited to determine how small RNAs carried by seminal exosomes contribute to the immunoregulatory and immunosuppressive functions of semen," says Dr. Vojtech. "Revealing specific mechanisms by which semen interferes with immune responses in the recipient female genital tract will be helpful to devise better strategies that prevent and treat sexually transmitted infections, including vaccination against HIV."

[Vojtech L, Woo S, Hughes S, Levy C, Ballweber L, Sauteraud RP, Strobl J, Westerberg K, Gottardo R, Tewari M, Hladik F](#). 2014. Exosomes in human semen carry a distinctive repertoire of small non-coding RNAs with potential regulatory functions. *Nucleic Acids Res*. DOI: 10.1093/nar/gku347 [Epub ahead of print]

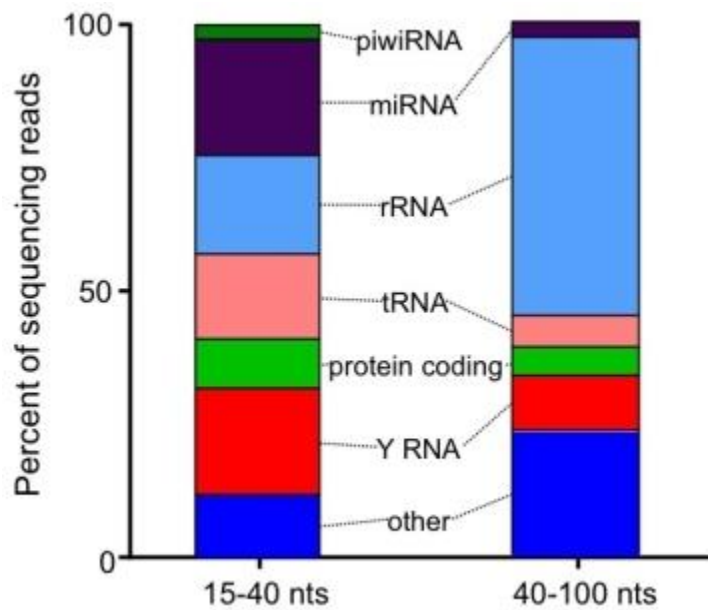


Image courtesy of Dr. Lucia Vojtech.

Distribution of RNA biotypes in RNA libraries of two size groups (15–40 nts and 40–100 nts). Segments of the bars indicate the percent of sequencing reads attributed to each RNA biotype among all RNA reads that mapped perfectly to known sequences, averaged across six semen donors.