Figure S1: Characterization of exosomes and their RNAs contents. Exosomes were isolated from HUVECs supernatant and purified by ultracentrifugation (A) The size distribution of exosomes assessed by dynamic light scattering (DLS). (B) Western Blotting for proteins known to be enriched in exosomes (the tetraspanins CD9, CD63 and CD81), a protein common in cells and exosomes (ANXA2) and the exclusively cellular Cyt C and AGO2. 20 µg of exosomes and cells lysates were loaded on the gel. RNA profiles of cellular (C) and exosomal (D) were analyzed using bioanalyser pico chip.
Figure S2: Principal component analysis (PCA) of total (long) and short RNA libraries from both cellular (CL) and exosomal (EX) samples. Samples were mapped against the human genome (GRCh38) and annotated to all RNA types prior PCA analysis.
| Sequence Logo | RNA class          | % Abundance Sequence per compartment | % Abundance Sequence in background | p-value    |
|---------------|--------------------|--------------------------------------|----------------------------------|------------|
| Genes only found in Cells |                    |                                      |                                  |            |
| ![Sequence Logo](image1) | Antisense RNAs     | 4.4                                  | 0.74                             | 1·10e-12   |
| ![Sequence Logo](image2) | lincRNAs           | 9.09                                 | 1.09                             | 1·10e-17   |
| ![Sequence Logo](image3) |                   | 11.14                                | 2.12                             | 1·10e-14   |
| ![Sequence Logo](image4) |                   | 9.09                                 | 1.52                             | 1·10e-13   |
| ![Sequence Logo](image5) |                   | 9.68                                 | 1.99                             | 1·10e-12   |
| ![Sequence Logo](image6) | piwi RNAs          | 24.83                                | 7.29                             | 1·10e-17   |
| ![Sequence Logo](image7) | Processed transcript RNAs | 28.12                                | 7.45                             | 1·10e-18   |
| ![Sequence Logo](image8) |                   | 16.07                                | 2.64                             | 1·10e-15   |
| ![Sequence Logo](image9) |                   | 20.98                                | 4.91                             | 1·10e-14   |
| ![Sequence Logo](image10) |                   | 29.91                                | 10.40                            | 1·10e-13   |
| ![Sequence Logo](image11) |                   | 20.54                                | 5.17                             | 1·10e-13   |
| ![Sequence Logo](image12) |                   | 19.64                                | 5.13                             | 1·10e-12   |
| ![Sequence Logo](image13) |                   | 11.61                                | 1.65                             | 1·10e-12   |
| ![Sequence Logo](image14) |                   | 21.88                                | 6.50                             | 1·10e-12   |
| Genes only found in Exosomes |                    |                                      |                                  |            |
| ![Sequence Logo](image15) | Antisense RNAs     | 10.36                                | 1.47                             | 1·10e-13   |
| ![Sequence Logo](image16) | lincRNAs           | 7.27                                 | 1.11                             | 1·10e-18   |
| ![Sequence Logo](image17) |                   | 5.85                                 | 0.70                             | 1·10e-17   |
| ![Sequence Logo](image18) |                   | 7.45                                 | 1.26                             | 1·10e-17   |
| ![Sequence Logo](image19) |                   | 12.23                                | 3.60                             | 1·10e-16   |
| Sequence Logo | RNA class | % Abundance Sequence per compartment | % Abundance Sequence in background | p-value |
|---------------|-----------|-------------------------------------|-----------------------------------|---------|
|               | Genes only found in Exosomes (continuation) |                                 |                                  |         |
|               | LincRNAs (continuation) |                                 |                                  |         |
|               | Processed Transcript RNA |                                 |                                  |         |
| AA GA UA GA CA AGU | 5.32 | 0.68 | 1.10e-15 |
| CU WU CA ACC | 20.39 | 8.96 | 1.10e-15 |
| CU WA AA UG GA AG | 4.26 | 0.40 | 1.10e-14 |
| GA AC GG CA AC | 7.98 | 1.81 | 1.10e-14 |
| UAA AC CU UC AG | 6.74 | 1.38 | 1.10e-13 |
| WC UC CA AU CA | 6.03 | 1.18 | 1.10e-12 |
| CC UC AU CU AU | 3.90 | 0.44 | 1.10e-12 |
| UC UC GC AU AC | 2.84 | 0.17 | 1.10e-12 |
| CA UC AG CC CC CU | 3.72 | 0.40 | 1.10e-12 |
| GC CC CA AG GG UC | 23.01 | 1.43 | 1.10e-20 |
| CA GA UC UC AC CA | 25.66 | 2.68 | 1.10e-18 |
| GC CA AU GG UG AU | 23.01 | 2.11 | 1.10e-17 |
| CC UC CC UC CA GU | 23.01 | 2.23 | 1.10e-16 |
| GG GA AA GA AG GC | 18.58 | 1.45 | 1.10e-15 |
| GG GG AA CC UC CA | 336.3 | 7.16 | 1.10e-14 |
| WC GC GG AU UC | 21.24 | 2.43 | 1.10e-14 |
| AC CA AU UG GG G | 15.93 | 1.19 | 1.10e-13 |
| CA UU GC UC AA CA | 18.58 | 1.97 | 1.10e-12 |
| GC GC GC GC GC GC | 23.01 | 3.49 | 1.10e-12 |
| AG GG GC CC UA CC UC GG | 15.04 | 1.12 | 1.10e-12 |
| Sequence Logo | RNA class | % Abundance Sequence per compartment | % Abundance Sequence in background | p-value |
|---------------|-----------|-------------------------------------|-----------------------------------|---------|
| **Genes only found in Exosomes (continuation)** | mRNA | 5.72 | 2.19 | 1·10e-16 |
| | | 3.29 | 0.91 | 1·10e-14 |
| | | 5.23 | 2.18 | 1·10e-12 |
| **Genes found in cells and exosomes significantly more present in cells** | lincRNAs | 20.61 | 8.56 | 1·10e-48 |
| | | 13.81 | 4.63 | 1·10e-45 |
| | | 16.18 | 6.67 | 1·10e-38 |
| | | 17.98 | 8.03 | 1·10e-37 |
| | | 14.58 | 5.87 | 1·10e-36 |
| | | 16.59 | 7.41 | 1·10e-34 |
| | | 14.06 | .547 | 1·10e-33 |
| | | 12.98 | 5.05 | 1·10e-33 |
| | | 12.83 | 4.98 | 1·10e-33 |
| | | 50.03 | 35.45 | 1·10e-33 |
| | | 13.14 | 5.45 | 1·10e-30 |
| | | 23.24 | 12.77 | 1·10e-30 |
| | | 15.15 | 6.87 | 1·10e-29 |
| | | 8.14 | 2.48 | 1·10e-29 |
| | | 15.56 | 7.18 | 1·10e-29 |
| | | 15.10 | 6.78 | 1·10e-29 |
| Sequence Logo | RNA class | % Abundance Sequence per compartment | % Abundance Sequence in background | p-value |
|---------------|-----------|-------------------------------------|-----------------------------------|---------|
| lincRNAs      |           |                                     |                                   |         |
| Genes found in cells and exosomes significantly more present in cells (continuation) |
|               |           | 12.93 | 5.49 | 1.0e-28 |
|               |           | 12.26 | 5.09 | 1.0e-28 |
|               |           | 13.70 | 6.07 | 1.0e-28 |
|               |           | 22.31 | 12.41| 1.0e-28 |
|               |           | 11.54 | 4.56 | 1.0e-28 |
|               |           | 24.47 | 14.14| 1.0e-28 |
|               |           | 16.54 | 8.16 | 1.0e-27 |
|               |           | 7.11  | 2.07 | 1.0e-27 |
|               |           | 34.16 | 22.89| 1.0e-24 |
|               |           | 31.12 | 20.35| 1.0e-24 |
|               |           | 4.17  | 0.82 | 1.0e-24 |
|               |           | 11.64 | 5.17 | 1.0e-23 |
|               |           | 11.23 | 4.96 | 1.0e-23 |
|               |           | 25.81 | 16.19| 1.0e-22 |
|               |           | 35.03 | 24.20| 1.0e-22 |
|               |           | 18.70 | 10.60| 1.0e-21 |
|               |           | 25.76 | 16.40| 1.0e-21 |
|               |           | 22.93 | 14.07| 1.0e-21 |
|               |           | 19.84 | 11.70| 1.0e-20 |
|               |           | 3.92  | 0.86 | 1.0e-20 |
| Sequence Logo | RNA class | % Abundance Sequence per compartment | % Abundance Sequence in background | p-value   |
|---------------|-----------|-------------------------------------|-----------------------------------|----------|
| UGCCACGUGG    | lincRNAs (continuation) | 29.06 | 19.47 | 1·10e-20 |
| CAGCCAUGUGGA  | lincRNAs (continuation) | 5.98  | 2.00  | 1·10e-19 |
| AAGCACAU       | lincRNAs (continuation) | 7.57  | 3.19  | 1·10e-17 |
| AGAUGUGUCUGA   | lincRNAs (continuation) | 15.61 | 9.14  | 1·10e-16 |
| CCGAGCAGGCA    | lincRNAs (continuation) | 7.42  | 3.17  | 1·10e-16 |
| CUGUGUGU      | lincRNAs (continuation) | 7.42  | 3.18  | 1·10e-16 |
| UGGUGGG       | lincRNAs (continuation) | 30.29 | 21.99 | 1·10e-14 |
| UCUCUCACCAG    | Processed transcript RNAs | 19.82 | 8.67  | 1·10e-21 |
| GCUGUGUUA      | Processed transcript RNAs | 23.91 | 12.07 | 1·10e-19 |
| UCUGUGGG       | Processed transcript RNAs | 29.87 | 16.87 | 1·10e-19 |
| UCUGUGACGCCC   | Processed transcript RNAs | 14.22 | 5.43  | 1·10e-18 |
| UGAUUUGUG       | Processed transcript RNAs | 16.09 | 6.82  | 1·10e-18 |
| GWUGCGAG       | Processed transcript RNAs | 25.07 | 13.49 | 1·10e-17 |
| AGUAACUCACUGG   | Processed transcript RNAs | 22.22 | 11.35 | 1·10e-17 |
| CAAGGGUUCU      | Processed transcript RNAs | 19.38 | 9.32  | 1·10e-17 |
| UACGUAAGGUW     | Processed transcript RNAs | 12.00 | 4.49  | 1·10e-16 |
| AACUCCCCAG      | Processed transcript RNAs | 17.33 | 8.12  | 1·10e-16 |
| AGCACCUUCU      | Processed transcript RNAs | 35.73 | 23.20 | 1·10e-15 |
| UCCAGGCC       | Processed transcript RNAs | 29.33 | 17.79 | 1·10e-15 |
| AAUCUGAGA       | Processed transcript RNAs | 62.67 | 49.03 | 1·10e-15 |
| Sequence Logo | RNA class | % Abundance Sequence per compartment | % Abundance Sequence in background | p-value |
|---------------|-----------|-------------------------------------|-----------------------------------|---------|
| Genes found in cells and exosomes significantly more present in cells (continuation) | | |
| GAACAAAGGAGGG | | 13.60 | 5.88 | 1·10e-14 |
| UAUCUGAAGC | | 11.47 | 4.50 | 1·10e-14 |
| GAGUCAAUU | | 18.49 | 9.45 | 1·10e-14 |
| UAGUGUGUA | | 15.56 | 7.31 | 1·10e-14 |
| AGGGGGCUCAG | | 18.93 | 9.93 | 1·10e-13 |
| AUUCCCAAGCCAU | | 22.58 | 12.81 | 1·10e-13 |
| CACCCACAGGCAC | | 12.62 | 5.59 | 1·10e-13 |
| UGACACUGGCA | | 19.91 | 10.95 | 1·10e-13 |
| UGACACUGGCA | | 14.49 | 7.10 | 1·10e-12 |
| Processed transcript RNAs (continuation) | | | | |
| Genes found in cells and exosomes significantly more present in exosomes | | |
| UCACAUUGG | | 54.49 | 37.74 | 1·10e-23 |
| CUCGACUUG | | 37.87 | 23.16 | 1·10e-21 |
| UCUUUAUGA | | 19.61 | 8.99 | 1·10e-21 |
| GAGGCUCAUGGG | | 22.19 | 10.86 | 1·10e-21 |
| CUUGUCACCCAGG | | 17.35 | 7.39 | 1·10e-20 |
| CUUGUCCUAAU | | 5.47 | 1.20 | 1·10e-18 |
| UCUCAAGAGUC | | 9.60 | 3.60 | 1·10e-18 |
| ACCAUUCAGGC | | 15.38 | 6.72 | 1·10e-17 |
| AUCAUGGCC | | 30.75 | 18.91 | 1·10e-16 |
| AGUCUUCAGGC | | 10.32 | 3.79 | 1·10e-16 |
| Antisense RNAs | | | | |
| Sequence Logo | RNA class | % Abundance Sequence per compartment | % Abundance Sequence in background | p-value |
|---------------|-----------|-------------------------------------|-----------------------------------|---------|
| **Genes found in cells and exosomes significantly more present in exosomes (continuation)** | | | | |
| GUCCUAUGCCCACA | Antisense RNAs (continuation) | 10.73 | 4.07 | 1·10e-15 |
| GAUAGCAGAACGUC | | 3.82 | 0.54 | 1·10e-15 |
| UGUCCUCACCU | | 62.23 | 48.53 | 1·10e-15 |
| CCGGGGCGCU | | 8.05 | 2.62 | 1·10e-14 |
| GAUCCAAUAUGU | | 3.82 | 0.62 | 1·10e-14 |
| AGUWGUGWCACA | | 5.78 | 1.55 | 1·10e-13 |
| UCACUGCA | | 35.71 | 24.22 | 1·10e-13 |
| AGAGAGAGACAG | | 44.17 | 32.27 | 1·10e-12 |
| CGGCCACUCUW | | 3.82 | 0.71 | 1·10e-12 |
| GGAGAACUGGCG | | 5.37 | 1.44 | 1·10e-12 |
| AGGGAUA | | 20.23 | 11.61 | 1·10e-12 |
| AGUCGCGC | | 16.92 | 9.07 | 1·10e-12 |
| AACACGCUC | | 15.89 | 8.34 | 1·10e-12 |
| GAAGCGUGAGAC | LincRNAs | 10.25 | 2.15 | 1·10e-50 |
| AGCAACACAUCUCA | | 10.54 | 2.32 | 1·10e-50 |
| AGUGGGGUGG | | 15.88 | 5.50 | 1·10e-45 |
| AGAACCAGAACC | | 14.35 | 4.63 | 1·10e-44 |
| AGUGAGAGUC | | 10.19 | 2.61 | 1·10e-41 |
| CAGGAGAGCC | | 10.19 | 2.94 | 1·10e-36 |
| ACUCUCAC | | 25.95 | 13.64 | 1·10e-35 |
| Sequence Logo | RNA class | % Abundance Sequence per compartment | % Abundance Sequence in background | p-value |
|---------------|-----------|--------------------------------------|-----------------------------------|---------|
| Genes found in cells and exosomes significantly more present in exosomes (continuation) |
| ![Sequence Logo](sequence_logo.png) | ![RNA Class](rna_class.png) | 9.14 | 2.58 | 1.10e-33 |
|  |  | 9.16 | 2.84 | 1.10e-33 |
|  |  | 5.54 | 0.93 | 1.10e-31 |
|  |  | 8.44 | 2.50 | 1.10e-29 |
|  |  | 19.68 | 10.23 | 1.10e-27 |
|  |  | 4.92 | 0.91 | 1.10e-27 |
|  |  | 6.56 | 1.67 | 1.10e-26 |
|  |  | 4.16 | 0.71 | 1.10e-24 |
|  |  | 10.54 | 4.21 | 1.10e-23 |
|  |  | 7.32 | 2.34 | 1.10e-22 |
|  |  | 6.91 | 2.21 | 1.10e-21 |
|  |  | 3.63 | 0.63 | 1.10e-21 |
|  |  | 3.63 | 0.64 | 1.10e-20 |
|  |  | 6.33 | 1.97 | 1.10e-20 |
|  |  | 4.16 | 0.95 | 1.10e-19 |
|  |  | 11.54 | 5.50 | 1.10e-18 |
|  |  | 2.87 | 0.44 | 1.10e-18 |
|  |  | 18.68 | 11.02 | 1.10e-18 |
|  |  | 4.22 | 1.05 | 1.10e-17 |
|  |  | 3.81 | 0.86 | 1.10e-17 |
| Sequence Logo | RNA class | % Abundance Sequence per compartment | % Abundance Sequence in background | p-value |
|---------------|-----------|-------------------------------------|-----------------------------------|---------|
| **Genes found in cells and exosomes significantly more present in exosomes (continuation)** | | | | |
| ![Sequence Logo](image1) | LincRNAs (continuation) | 59.17 | 48.63 | 1.10e-15 |
| ![Sequence Logo](image2) | | 12.19 | 6.36 | 1.10e-15 |
| ![Sequence Logo](image3) | | 12.54 | 6.64 | 1.10e-15 |
| ![Sequence Logo](image4) | | 7.26 | 3.14 | 1.10e-14 |
| ![Sequence Logo](image5) | | 12.30 | 6.78 | 1.10e-13 |
| ![Sequence Logo](image6) | | 2.17 | 0.35 | 1.10e-13 |
| ![Sequence Logo](image7) | | 4.80 | 1.69 | 1.10e-13 |
| ![Sequence Logo](image8) | Processed transcript RNAs | 17.78 | 4.40 | 1.10e-19 |
| ![Sequence Logo](image9) | | 14.81 | 3.43 | 1.10e-17 |
| ![Sequence Logo](image10) | | 28.89 | 11.87 | 1.10e-17 |
| ![Sequence Logo](image11) | | 29.14 | 12.20 | 1.10e-16 |
| ![Sequence Logo](image12) | | 16.79 | 4.66 | 1.10e-16 |
| ![Sequence Logo](image13) | | 29.63 | 12.78 | 1.10e-16 |
| ![Sequence Logo](image14) | | 22.96 | 8.42 | 1.10e-15 |
| ![Sequence Logo](image15) | | 14.07 | 3.53 | 1.10e-15 |
| ![Sequence Logo](image16) | | 11.36 | 2.27 | 1.10e-15 |
| ![Sequence Logo](image17) | | 23.95 | 9.38 | 1.10e-14 |
| ![Sequence Logo](image18) | | 11.85 | 2.50 | 1.10e-14 |
| ![Sequence Logo](image19) | | 14.81 | 3.96 | 1.10e-14 |
| ![Sequence Logo](image20) | | 17.78 | 6.01 | 1.10e-13 |
### Genes found in cells and exosomes significantly more present in exosomes (continuation)

| Sequence Logo | RNA class | % Abundance Sequence per compartment | % Abundance Sequence in background | p-value    |
|---------------|-----------|-------------------------------------|-----------------------------------|------------|
|               | Processed transcript RNA (continuation) | 11.85 | 2.93 | 1·10e-12 |
|               |                                                     | 15.80 | 5.13 | 1·10e-12 |
|               |                                                     | 15.31 | 4.92 | 1·10e-12 |
|               |                                                     | 12.35 | 3.30 | 1·10e-12 |

Figure S3:
RNA motifs found exclusively present in cells, exosomes or in both compartments.
After segregating the genes by RNA class and localization (only in cells or in exosomes, or common in both compartments but significantly enriched in one of them), HOMER was used to find enriched sequences.
This table shows all the significantly enriched motifs found per RNA class and compartment and the relative abundance of the motifs in the selected compartment compared to the background (all genes found in any compartment for each specific RNA class).