SUPPLEMENTARY TABLES

Supplementary Table 1. HDL-miRNA levels (mean) by real-time PCR TaqMan assays, as reported by relative quantitative values (RQV).

Supplementary Table 2. Multivariate analysis of sRNA profiles compared to liver profiles (WT only).

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SUPPLEMENTARY FIGURES
Supplementary Figure 1. Distribution of cholesterol, protein, and triglycerides across size-exclusion fractions. (A-C) Colorimetric assays for (A) total cholesterol, (B) total protein, and (C) triglycerides.). Wild-type, WT (blue); Scavenger receptor BI Knockout mice (Scarb1−/−), SR-BI KO (red). Size-exclusion chromatography fractions used to isolate HDL and APOB particles. mg, milligrams. HDL WT, N=7; HDL SR-BI KO N=7; APOB WT, N=7, APOB SR-BI KO N=7; Liver WT, N=7; Liver SR-BI KO, N=7; Bile WT, N=7; Bile SR-BI KO, N=6; Urine WT, N=5; Urine SR-BI KO, N=6.

Supplementary Figure 2. Expression of miRNA 5’ isomiRs and 3’ NTAs across sample types. WT, wild-type mice; SR-BI KO, Scavenger receptor BI Knockout mice (Scarb1−/−). (A) Pie charts illustrating the fraction of miRNA 5’ isomiRs (red) per total miRNA reads. (B-C) sRNA-seq analysis of miRNA (B) 5’ isomiRs and (C) 3’ non-templated additions (NTA). Mean ±S.E.M. Student’s t-tests. *p<0.05. HDL WT, N=7; HDL SR-BI KO N=7; APOB WT, N=7, APOB SR-BI KO N=7; Liver WT, N=7; Liver SR-BI KO, N=7; Bile WT, N=7; Bile SR-BI KO, N=6; Urine WT, N=5; Urine SR-BI KO, N=6.

Supplementary Figure 3. Positional coverage analysis of host tDRs based on parent tRNA amino acid anticodons. Signal (red) represents mean coverage percentage across parent length. WT, wild-type mice; SR-BI KO, Scavenger receptor BI Knockout mice (Scarb1−/−). HDL WT, N=7; HDL SR-BI KO N=7; APOB WT, N=7, APOB SR-BI KO N=7; Liver WT, N=7; Liver SR-BI KO, N=7; Bile WT, N=7; Bile SR-BI KO, N=6; Urine WT, N=5; Urine SR-BI KO, N=6.
Supplementary Figure 4. Classification of host tDRs based on parent tRNA amino acid anticodons. WT, wild-type mice; SR-BI KO, Scavenger receptor BI Knockout mice (Scarb1−/−).
(A) Normalized read counts for host tDRs (per million total reads) based parent tRNA amino acid anti-codons. (B) Pie charts illustrating the percent of host tDRs per total tDR counts for parent tRNA amino acid anticodons. HDL WT, N=7; HDL SR-BI KO N=7; APOB WT, N=7, APOB SR-BI KO N=7; Liver WT, N=7; Liver SR-BI KO, N=7; Bile WT, N=7; Bile SR-BI KO, N=6; Urine WT, N=5; Urine SR-BI KO, N=6.

Supplementary Figure 5. Hierarchical clustering of samples at parent RNA and fragment RNA levels of analysis. (A-H) Heatmap of hierarchical clustered pairwise correlation (Spearman, R) coefficients between group means for host sRNAs. (A) Parent tDR (B) Fragment tDR (C) Parent rDR (D) Fragment rDR (E) Parent snDR (F) Fragment snDR (G) Parent miscRNA (H) Fragment miscRNA. WT, wild-type mouse; SR-BI KO, Scavenger receptor BI Knockout mice (Scarb1−/−). HDL WT, N=7; HDL SR-BI KO N=7; APOB WT, N=7, APOB SR-BI KO N=7; Liver WT, N=7; Liver SR-BI KO, N=7; Bile WT, N=7; Bile SR-BI KO, N=6; Urine WT, N=5; Urine SR-BI KO, N=6.

Supplementary Figure 6. Fragment level analysis within sRNA classes increases resolution between sample types by Principal Coordinate Analysis. (A-F) Principal Coordinate Analysis (PCoA) of host sRNA profiles based on (A) parent rRNAs, (B) individual fragment rDRs, (C) parent snRNAs, (D) individual fragment snDRs, (E) parent miscellaneous RNAs (miscRNA), and (F) individual fragment miscRNAs for samples from WT (empty circles) and SR-BI KO
(filled circles) mice. NMDS1, Non-metric multidimensional scaling. WT, wild-type mice; SR-BI KO, Scavenger receptor BI Knockout mice \((Scarbi^{-/-})\). HDL WT, N=7; HDL SR-BI KO N=7; APOB WT, N=7, APOB SR-BI KO N=7; Liver WT, N=7; Liver SR-BI KO, N=7; Bile WT, N=7; Bile SR-BI KO, N=6; Urine WT, N=5; Urine SR-BI KO, N=6.

Supplementary Figure 7. Validation of multiple classes of host sRNAs identified by sRNA-seq of lipoproteins, biofluids and tissue. (A-D) Real-time PCR analysis of candidate sRNAs with predicted folding structures of parent RNAs for (A) mmu-miR-223-3p, (B) snDR_Gm26232, (C) snDR_Gm22866, and (D) miscellaneous RNA (miscRNA) Rpph1. WT (white circles), wild-type mice; SR-BI KO (red circles), Scavenger receptor BI Knockout mice \((Scarbi^{-/-})\). Of note, the buffer sample represents total RNA isolated from running buffer used in SEC to isolate lipoproteins. HDL WT, N=7; HDL SR-BI KO N=7; APOB WT, N=7, APOB SR-BI KO N=7; Liver WT, N=7; Liver SR-BI KO, N=7; Bile WT, N=7; Bile SR-BI KO, N=6; Urine WT, N=5; Urine SR-BI KO, N=6.

Supplementary Figure 8. Positional coverage analysis of host snDRs based on parent snRNAs. Signal (red) represents mean coverage percentage across parent length. WT, wild-type mice; SR-BI KO, Scavenger receptor BI Knockout mice \((Scarbi^{-/-})\). HDL WT, N=7; HDL SR-BI KO N=7; APOB WT, N=7, APOB SR-BI KO N=7; Liver WT, N=7; Liver SR-BI KO, N=7; Bile WT, N=7; Bile SR-BI KO, N=6; Urine WT, N=5; Urine SR-BI KO, N=6.
Supplementary Figure 9. Lipoprotein sRNA profiles are highly-correlated for parent RNAs and
lowly-correlated for individual sRNAs fragments. Heatmaps of correlation coefficients 
(Spearman, R) for host sRNA parents and individual fragments across samples within each group
for miRNAs, rDRs, snDRs, and snoDRs. WT, wild-type mice; SR-BI KO, Scavenger receptor BI
Knockout mice (Scarb1−/−). HDL WT, N=7; HDL SR-BI KO N=7; APOB WT, N=7, APOB SR-
BI KO N=7; Liver WT, N=7; Liver SR-BI KO, N=7; Bile WT, N=7; Bile SR-BI KO, N=6;
Urine WT, N=5; Urine SR-BI KO, N=6.

Supplementary Figure 10. Lipoproteins are enriched with exogenous tDR’s, primarily linked to
bacteria. (A) Abundance of non-host tDRs based on parent tRNA transcripts (database) across
kingdoms and higher organizations, as reported as reads per million total reads (RPM). Two-way
ANOVA Tukey's multiple comparisons test. *p<0.05. (B-C) Stacked bar plots of non-host tDRs
aligned to parent rRNAs across kingdoms and higher organizations, as reported as mapped reads
per million total reads for (B) bacterial species and (C) parent tRNA amino acid anti-codons.
WT, wild-type mice; SR-BI KO, Scavenger receptor BI Knockout mice (Scarb1−/−). HDL WT,
N=7; HDL SR-BI KO N=7; APOB WT, N=7, APOB SR-BI KO N=7; Liver WT, N=7; Liver
SR-BI KO, N=7; Bile WT, N=7; Bile SR-BI KO, N=6; Urine WT, N=5; Urine SR-BI KO, N=6.

Supplementary Figure 11. Positional coverage maps of non-host tDRs in tissue and biofluids.
Positional coverage maps of non-host tDRs for parent tRNA amino acid anti-codons, as reported
as mean cumulative read fractions (read counts / total counts) for liver, bile, and urine. WT, wild-
type mice; SR-BI KO, Scavenger receptor BI Knockout mouse (Scarb1−/−). HDL WT, N=7; HDL
SR-BI KO, N=7; APOB WT, N=7, APOB SR-BI KO, N=7; Liver WT, N=7; Liver SR-BI KO, N=7; Bile WT, N=7; Bile SR-BI KO, N=6; Urine WT, N=5; Urine SR-BI KO, N=6.

Supplementary Figure 12. Positional coverage analysis of non-host tDRs based on parent tRNA amino acid anticodons. Signal (red) represents mean coverage percentage across parent length. WT, wild-type mice; SR-BI KO, Scavenger receptor BI Knockout mice (Scarb1−/−). HDL WT, N=7; HDL SR-BI KO N=7; APOB WT, N=7, APOB SR-BI KO N=7; Liver WT, N=7; Liver SR-BI KO, N=7; Bile WT, N=7; Bile SR-BI KO, N=6; Urine WT, N=5; Urine SR-BI KO, N=6.

Supplementary Figure 13. Lipoproteins are enriched with non-host rDRs. (A) Abundance of non-host rDRs based on parent rRNA transcripts (database) across kingdoms and higher organizations, as reported as reads per million total reads (RPM).

Supplementary Figure 14. TIGER identifies bacterial species that likely contribute bacterial sRNA to sRNA-seq of lipoproteins and biofluids. WT, wild-type mice; SR-BI KO, Scavenger receptor BI Knockout mice (Scarb1−/−). (A) Stacked bar plots of non-host sRNAs aligned to bacterial genomes in the human microbiome project (HMB), as reported as mapped reads per million total reads. (B-C) Pie charts illustrating the distribution of genome counts per total bacterial reads for species in the (C) HMB and (C) environment (ENV). (D) Stacked bar plots of non-host sDRs aligned to ENV bacterial genomes, as reported as mapped reads per million total reads. HDL WT, N=7; HDL SR-BI KO N=7; APOB WT, N=7, APOB SR-BI KO N=7; Liver.
Supplementary Figure 15. Lipoproteins are enriched for proteobacteria sRNAs. WT, wild-type mice; SR-BI KO, Scavenger receptor BI Knockout mice (Scarb1<sup>−/−</sup>). (A-C) Circular tree maps for non-host bacterial sRNAs on lipoproteins from WT mice, as organized by taxonomy – proteobacteria, green; actinobacteria, blue; firmicutes, yellow; bacteroidetes, red. Maps were generated from bacterial counts organized by species within the human microbiome project (HMB) on (A) APOB particles and bacterial species in the environment (ENV) on (B) HDL and (C) APOB particles. Diameter is proportional to the mean number of reads at the genome level (counts). HDL WT, N=7; APOB WT, N=7

Supplementary Figure 16. TIGER identifies distinct contributions from microbiome and environmental bacterial genome modules. Pie charts illustrating alignment overlap for non-host bacterial genome reads between species in the human microbiome project or environment. HDL WT, N=7; HDL SR-BI KO N=7; APOB WT, N=7, APOB SR-BI KO N=7; Liver WT, N=7; Liver SR-BI KO, N=7; Bile WT, N=7; Bile SR-BI KO, N=6; Urine WT, N=5; Urine SR-BI KO, N=6.

Supplementary Figure 17. TIGER identifies fungal genomes as potential contributors to lipoprotein sRNA-seq. WT, wild-type mice; SR-BI KO, Scavenger receptor BI Knockout mice (Scarb1<sup>−/−</sup>). (A) Stacked bar plots of non-host sRNAs aligned to fungal genomes, as reported as mapped reads per million total reads. (B) Pie charts illustrating the distribution of genome counts.
per total fungal reads. HDL WT, N=7; HDL SR-BI KO N=7; APOB WT, N=7, APOB SR-BI KO N=7; Liver WT, N=7; Liver SR-BI KO, N=7; Bile WT, N=7; Bile SR-BI KO, N=6; Urine WT, N=5; Urine SR-BI KO, N=6.

Supplementary Figure 18. Small RNA aligned to exogenous modules by TIGER are not likely to be misidentified host sRNA. All reads that were aligned within any exogenous sRNA modules were compiled and allowed to align to the host genome (mouse) with either 0, 1 or 2 mismatches. Results of host mapping are presented as total counts (top) and by percentage (bottom). WT, wild-type mice; SR-BI KO, Scavenger receptor BI Knockout mice (Scarb1−/−).

HDL WT, N=7; HDL SR-BI KO N=7; APOB WT, N=7, APOB SR-BI KO N=7; Liver WT, N=7; Liver SR-BI KO, N=7; Bile WT, N=7; Bile SR-BI KO, N=6; Urine WT, N=5; Urine SR-BI KO, N=6.

Supplementary Figure 19. Distinct length distributions of putative fungal sRNA trafficked by lipoproteins. Distribution of read lengths, as reported as reads per million total reads, for non-host fungal sRNAs. Two-tailed Student’s t-tests. *p<0.05. HDL WT, N=7; HDL SR-BI KO N=7; APOB WT, N=7, APOB SR-BI KO N=7; Liver WT, N=7; Liver SR-BI KO, N=7; Bile WT, N=7; Bile SR-BI KO, N=6; Urine WT, N=5; Urine SR-BI KO, N=6.

Supplementary Figure 20. Bacterial sRNA fragments resolve APOB sRNA from HDL sRNA in Principal Coordinate Analysis. (A-D) Principal Coordinate Analysis (PCoA) of non-host bacterial sRNA profiles based on (A) genome counts for species in the human microbiome
project (HMB), (B) individual fragment counts for HMB, (C) genome counts for species in the environment (ENV), (D) individual fragment counts for ENV. NMDS1, Non-metric multidimensional scaling. WT (empty circles), wild-type mice; SR-BI KO (filled circles), Scavenger receptor BI Knockout mice (Scarb1⁻/⁻). HDL WT, N=7; HDL SR-BI KO N=7; APOB WT, N=7, APOB SR-BI KO N=7.

Supplementary Figure 21. Alignment of candidate (bacterial) sRNA to Pseudomonas fluorescens 23S rRNA.

Supplementary Figure 22. Alignment of candidate (bacterial) sRNA to Janthinobacterium lividum 23S rRNA.

Supplementary Figure 23. HDL and APOB particles transport a non-host fungal sRNA. Alignment of candidate (fungal) sRNA to Verticillium 18S rRNA. Real-time PCR analysis of candidate non-host fungal sRNA for exogenous rDR Verticillium (exo_rDR_Vsp). WT (white circles), wild-type mice; SR-BI KO (red circles), Scavenger receptor BI Knockout mice (Scarb1⁻/⁻). Of note, buffer corresponds to total RNA isolated from the SEC running buffer used to isolate lipoproteins from plasma. HDL WT, N=7; HDL SR-BI KO N=7; APOB WT, N=7, APOB SR-BI KO N=7; Liver WT, N=7; Liver SR-BI KO, N=7; Bile WT, N=7; Bile SR-BI KO, N=6; Urine WT, N=5; Urine SR-BI KO, N=6.
Supplementary Figure 24. Class independent analysis of the most abundant sRNA of each sample type identifies distinct clustering by group. Heatmap of hierarchical clustered pairwise correlation (Spearman, R) coefficients between group means for the top ranked (collective top 100 non-redundant) sRNAs for each group. WT, wild-type mice; SR-BI KO, Scavenger receptor BI Knockout mice (Scarb1−/−). HDL WT, N=7; HDL SR-BI KO N=7; APOB WT, N=7, APOB SR-BI KO N=7; Liver WT, N=7; Liver SR-BI KO, N=7; Bile WT, N=7; Bile SR-BI KO, N=6; Urine WT, N=5; Urine SR-BI KO, N=6.

Supplementary Figure 25. TIGER pipeline comparison for canonical miRNA analysis. (A) sRNA-seq analysis of canonical miRNAs for different pipelines, as reported as miRNAs Reads Per Million (RPM) total reads, for WT HDL, APOB, and liver samples. (B) Correlations between different analysis pipelines for canonical miRNAs in WT HDL, APOB, and liver samples. Spearman correlation. HDL WT, N=7; APOB WT, N=7, Liver WT, N=7.

Supplementary Figure 26. TIGER analysis of Escherichia coli lysates, growth media (LB) and isolated extracellular outer membrane vesicles (ExOMV) samples. Sample descriptions provided in original manuscript by Ghosal et al. (PMID: 25611733). Intra = E. coli total cell lysate RNA; ExOMV = Extracellular outer membrane vesicles; ExOMV_free = cultured media after removal of ExOMV; LB = uncultured bacterial growth media; LB_cultured = cell free bacterial growth media after culture. A) Summary of alignment results to host genome modules (E. coli strain K-12) and non-host modules. B) Summary of phyla represented in alignment to exogenous tRNA
Supplementary Figure 27. TIGER analysis of sRNA-seq of human plasma samples obtained from healthy (norm), ulcerative colitis (uc), or colorectal cancer (crc) subjects, originally described by Wang et al. (PMID: 23251414). **A)** Summary of alignment results to host genome modules (human) and non-host modules. Also presented are reads that were not aligned to host sRNA, but were too short for exogenous sRNA analysis (<20 nt in length) and reads that were unmapped. **B)** Relative amounts of host and non-host sRNA identified by TIGER. **C)** Summary of phyla represented in alignment to exogenous tRNA and **D)** rRNA databases. **E)** Summary of fungal species detected by alignment to fungal genome database. **F)** Summary of bacterial phyla identified by mapping to bacterial genomes of the human microbiome (HMB) and **G)** bacterial genomes of the environment (ENV). **H)** Relative percentage of bacterial reads mapping to HMB module, ENV module or both.

Supplementary Figure 28. Differential expression of parent snRNA, snoRNA and miscRNA and their fragments. Differential expression analysis by DEseq2. Volcano plots demonstrating significant (adjusted p>0.05) differential (>1.5-absolute fold change) abundances for snDRs, snoDRs, and other sRNAs (osDRs a.k.a. miscellaneous RNAs) at the parent and individual fragment levels - red, increased; blue, decreased. WT, wild-type mice; SR-BI KO, Scavenger receptor BI Knockout mice (Scarb1−/−). HDL WT, N=7; HDL SR-BI KO N=7; APOB WT, N=7,
APOB SR-BI KO, N=7; Liver WT, N=7; Liver SR-BI KO, N=7; Bile WT, N=7; Bile SR-BI KO, N=6; Urine WT, N=5; Urine SR-BI KO, N=6.

Supplementary Figure 29. Differential expression of exogenous genomes and exogenous sRNA fragments identified by TIGER. Differential expression analysis by DEseq2. Volcano plots of demonstrating significant (adjusted p>0.05) differential (>1.5-absolute fold change) abundances for non-host bacterial sRNAs at the genome and individual fragment levels for A) HMB module, B) ENV module and C) fungal module - red, increased; blue, decreased. WT, wild-type mice; SR-BI KO, Scavenger receptor BI Knockout mice (Scarb1/−). HDL WT, N=7; HDL SR-BI KO N=7; APOB WT, N=7, APOB SR-BI KO, N=7; Liver WT, N=7; Liver SR-BI KO, N=7; Bile WT, N=7; Bile SR-BI KO, N=6; Urine WT, N=5; Urine SR-BI KO, N=6.

Supplementary Figure 30. Differential expression of only the top most abundant sRNAs on lipoproteins within the class-independent module. Differential expression analysis by DEseq2. Volcano plots of demonstrating significant (adjusted p>0.05) differential (>1.5-absolute fold change) abundances for the top most abundant (collective top 100 non-redundant) sRNAs at the independent of class and contributing species between wild-type (WT) and Scavenger receptor BI Knockout mice (Scarb1/−) (SR-BI KO) mice - red, increased; blue, decreased. HDL WT, N=7; HDL SR-BI KO N=7; APOB WT, N=7, APOB SR-BI KO, N=7; Liver WT, N=7; Liver SR-BI KO, N=7; Bile WT, N=7; Bile SR-BI KO, N=6; Urine WT, N=5; Urine SR-BI KO, N=6.
Supplementary Figure 31. Contaminant bacterial DNA is not present in tested plasma samples. To assess the possibility that bacterial sRNA were the result of contamination, we isolated total DNA from *E. coli*, reagent grade water and 30 uL of original plasma samples used in this study and measured the abundance of bacterial DNA by real-time PCR using a eubacteria primer set that amplifies a broadly conserved region of prokaryote rRNA. To establish relative concentrations, one ng of total *E.coli* DNA, and serial 5-fold dilutions, were used as positive controls. As a negative control, we performed mock DNA extractions of reagent-grade water. Resultant Ct were then normalized to water (RQV =1). Bacterial DNA input was then calculated by standard curve of positive controls.

Supplementary Figure 32. Human lipoproteins, but not buffer and RNA isolation column controls, are also enriched in exogenous sRNA. Purchased human plasma (EDTA isolated; n=2) was fractionated by SEC (500 µL input) in the same manner as mouse plasma. As was done in mice, cholesterol and triglyceride levels were used to identify HDL and APOB fractions, which were subsequently pooled and concentrated to a volume of 100 uL. As a negative control, buffer used for SEC was prepared in mock and Total RNA was isolated as described previously, except that 30 fM of synthetic Cel-miR-39 was spiked to each lipoprotein and buffer sample. As an additional negative control, RNAse free water was added to an additional column and eluted with other samples (no spike added). Data are results of real-time PCR for indicated endogenous and exogenous sRNA targets.
Supplementary Figure 33. Unfractionated mouse and human plasma samples have detectable levels of exogenous sRNA. Total RNA was isolated from mouse plasma (30 µL) of wild-type and SR-BI KO mice (n=10) used in this study or human plasma (50 µL; n=8) as described in Materials and Methods. Data are results of real-time PCR for indicated endogenous and exogenous sRNA targets. NTC = no template control (RNA elution buffer).