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RESEARCH ARTICLE

Recent evolution of the developing human intestine affects metabolic and barrier functions

BY QIANHUI YU, UMUT KILIK, *ET AL.* | 17 JUL 2025

Diet, microbiota, and other exposures place the intestinal epithelium as a nexus for evolutionary change; however, little is known about genomic changes associated with adaptation to a uniquely human environment. Here, we interrogate the evolution of cell types in the developing human intestine by comparing tissue and organoids from humans, chimpanzees, and mice. We find that recent changes in primates are associated with immune barrier function and lipid/xenobiotic metabolism, and that human-specific genetic features impact these functions. Enhancer assays, genetic deletion, and in silico mutagenesis resolve evolutionarily significant enhancers of Lactase (LCT) and Insulin-like Growth Factor Binding Protein 2 (IGFBP2). Altogether, we identify the developing human intestinal epithelium as a rapidly evolving system, and show that great ape organoids provide insight into human biology.

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RESEARCH ARTICLE

A hypoxia-responsive tRNA-derived small RNA confers renal protection through RNA autophagy

BY GUOPING LI, LINGFEI SUN, *ET AL.* | 17 JUL 2025

Transfer RNA-derived small RNAs (tsRNAs, or tDRs) perform a range of cellular functions. Here, we showed that a hypoxia-induced tDR, derived from the 3′ end of tRNA-Asp-GTC (tRNA-Asp-GTC-3′tDR), activated autophagic flux in kidney cells, while its silencing blocked autophagic flux. Functional gain/loss-of-function studies in murine kidney disease models demonstrated a significant reno-protective function of tRNA-Asp-GTC-3′tDR. Mechanistically, tRNA-Asp-GTC-3′tDR assembled stable G-quadruplex structures and sequestered pseudouridine synthase PUS7, preventing catalytic pseudouridylation of histone mRNAs. The resulting pseudouridylation deficiency directed histone mRNAs to the autophagosome-lysosome pathway, triggering RNA autophagy. This tDR-induced RNA autophagy pathway was activated during murine and human kidney diseases, suggesting clinical relevance. Thus, tRNA-Asp-GTC-3′tDR plays a role in regulating RNA autophagy, which helps to maintain homeostasis in kidney cells and protects against kidney injury.

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