

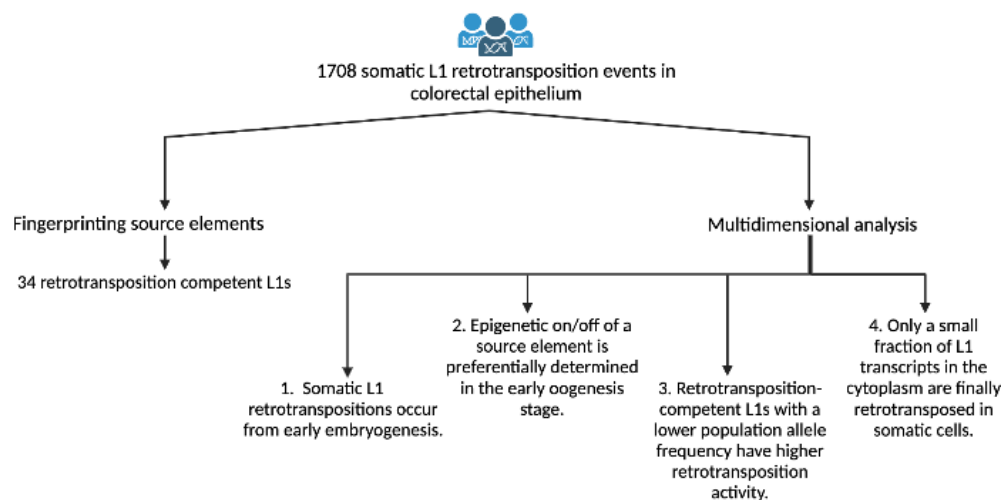
Editor's Choice**Editor's Selection of the Important Research Investigations in the Field of Molecular Medicine Communications from Around the World****Editorial Staff**

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L1 Retrotransposition in Normal Colorectal Epithelium

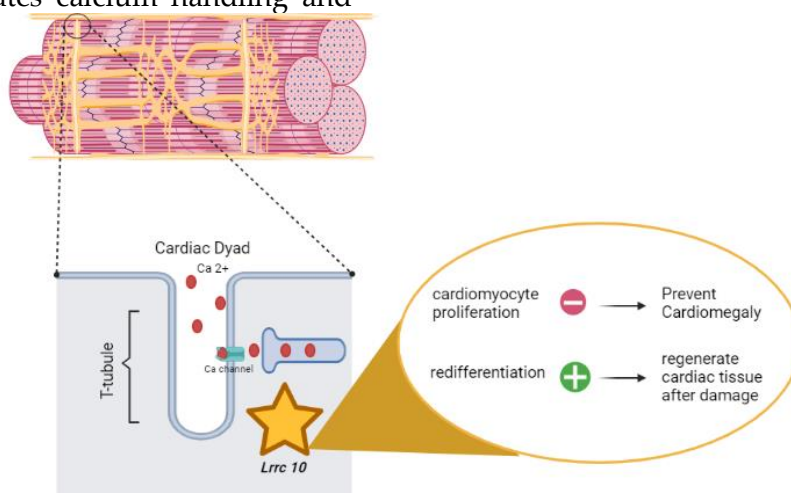
Somatic L1 retrotransposition refers to the process in which long interspersed nuclear elements (LINE-1 or L1 elements), which are a type of transposable element, move within the DNA of somatic cells. These elements can have the ability to "copy and paste" themselves into different genomic locations, potentially leading to genetic alterations. While L1 retrotransposition has been extensively studied in the context of cancer, it is still a topic of ongoing research to determine its prevalence and significance in normal tissues, including the colorectal epithelium. Colorectal epithelium refers to the tissue lining the colon and rectum, and abnormalities in this tissue can contribute to the development of colorectal cancer. Nam and

colleagues explored the whole-genome sequences of 899 single-cell clones established from three different cell types collected from 28 individuals. They found 1,708 somatic L1 retrotransposition events that were enriched in the colorectal epithelium and showed a positive relationship with age. Analysis of matched cancers further suggested that the somatic L1 retrotransposition rate is substantially increased during colorectal tumorigenesis. They concluded that L1 retrotransposition-induced somatic mosaicism in normal cells and provides insights into the genomic and epigenomic regulation of transposable elements over the human lifetime. *Nature*. 2023 May;617(7961):540-547. doi: 10.1038/s41586-023-06046-z.



Cardiomyocyte Maturation During Regeneration

The interplay between calcium signaling and sarcomeres plays a crucial role in directing cardiomyocyte maturation during cardiac regeneration. During cardiac regeneration, various processes occur to restore damaged or lost cardiac tissue, including the proliferation and differentiation of precursor cells into functional cardiomyocytes. These newly formed cardiomyocytes undergo a maturation process to acquire the structural and functional characteristics of adult cardiomyocytes. Nguyen and colleagues found that the cardiac dyad, a structure that regulates calcium handling and



Small Molecules for Chemically Induced Pluripotency Inception

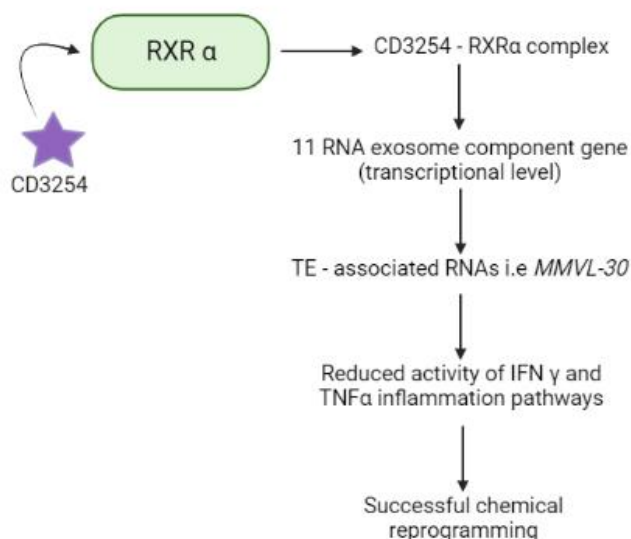
Harnessing endogenous transcription factors directly by small molecules for chemically induced pluripotency inception refers to using specific small molecules to activate endogenous transcription factors to reprogram adult cells into induced pluripotent stem cells (iPSCs). This approach aims to bypass the use of viral vectors or genetic manipulation to introduce exogenous factors, making it a potentially safer and more efficient method for generating iPSCs. Jin and colleagues show that small molecule CD3254 activates endogenous existing transcription factor RXR α to significantly promote mouse

excitation-contraction coupling, played a key role in the redifferentiation process. A component of the cardiac dyad called leucine-rich repeat-containing 10 (Lrrc10) acted as a negative regulator of proliferation, prevented cardiomegaly, and induced redifferentiation. They found that its function was conserved in mammalian cardiomyocytes. Their study highlights the importance of the underlying mechanisms required for heart regeneration and their application to the generation of fully functional cardiomyocytes. *Science*. 2023 May 19;380(6646):758-764. doi: 10.1126/science.abo6718.

chemical reprogramming. Mechanistically, the CD3254-RXR α axis can directly activate all the 11 RNA exosome component genes (*Exosc1-10* and *Dis3*) at the transcriptional level. Unexpectedly, rather than degrading mRNAs as its substrates, RNA exosome mainly modulates the degradation of transposable element (TE)-associated RNAs, particularly *MMVL30*, which is identified as a new barrier for cell-fate determination. In turn, *MMVL30*-mediated inflammation (IFN- γ and TNF- α pathways) is reduced, promoting successful reprogramming. Collectively, their study provides conceptual advances for translating environmental cues into pluripotency inception, particularly

identifies that the CD3254-RXR α -RNA exosome axis can promote chemical reprogramming and suggests modulation of TE-mediated inflammation via CD3254-inducible RNA exosome as important opportunities for

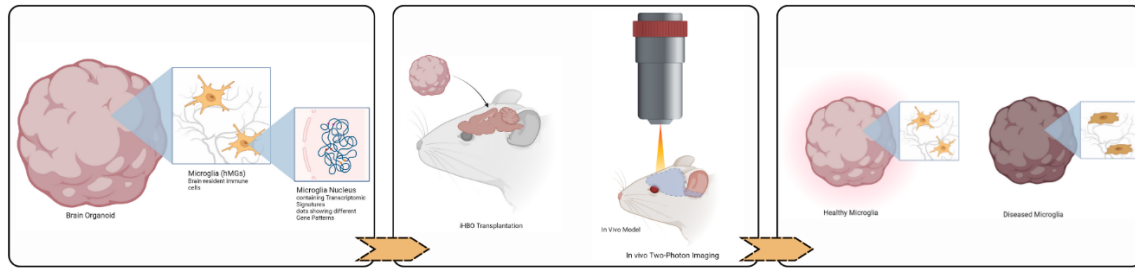
controlling cell fates and regenerative medicine. *Proc Natl Acad Sci USA*. 2023 May 23;120(21):e2215155120. doi: 10.1073/pnas.2215155120.



Study of Human Microglia Phenotypes via an *In Vivo* Neuroimmune Organoid Model

Microglia are specialized brain-resident macrophages that play crucial roles in brain development, homeostasis, and disease. However, until now, the ability to model interactions between the human brain environment and microglia has been severely limited. To overcome these limitations, Schafer and colleagues developed an *in vivo* xenotransplantation approach that allows us to study functionally mature human microglia (hMGs) that operate within a physiologically relevant, vascularized immunocompetent human brain organoid (iHBO) model. Developing an *in vivo* neuroimmune organoid model to study human microglia phenotypes would involve creating a three-dimensional structure that mimics the complexity of the human brain and immune system. Such a model could provide a valuable tool to investigate the

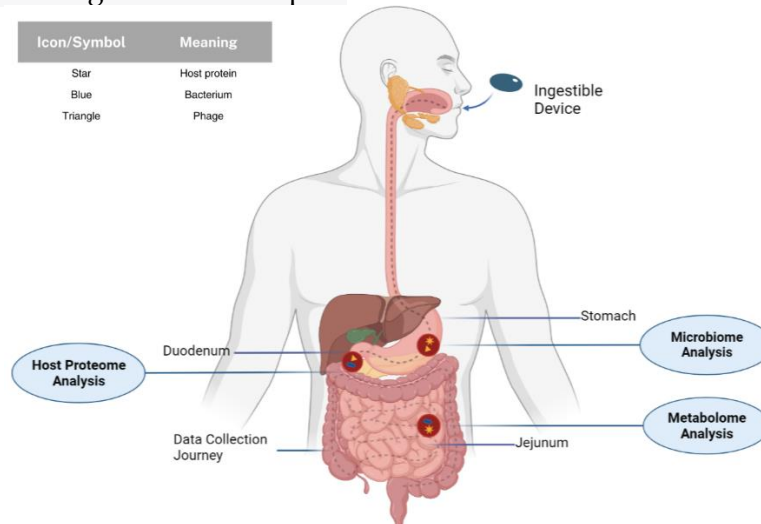
behavior and function of microglia, the resident immune cells of the central nervous system, in a more physiologically relevant context. Data from Schafer and colleagues show that organoid-resident hMGs gain human-specific transcriptomic signatures that closely resemble their *in vivo* counterparts. *In vivo* two-photon imaging reveals that hMGs actively engage in surveilling the human brain environment, react to local injuries, and respond to systemic inflammatory cues. Finally, they demonstrate that the transplanted iHBOs developed here offer the unprecedented opportunity to study functional human microglia phenotypes in health and disease and provide experimental evidence for a brain-environment-induced immune response in a patient-specific model of autism with macrocephaly. *Cell*. 2023 May 11;186(10):2111-2126.e20. doi: 10.1016/j.cell.2023.04.022.



Study of the Human Microbiota Under Physiological Conditions

Profiling the human intestinal environment under physiological conditions involves characterizing the various components and factors in the gut to understand its normal functioning. This profiling can encompass

multiple aspects, including the microbiome, host immune response, metabolites, and the physical environment of the intestine. Shalon and colleagues developed an ingestible device that collects samples from multiple regions of the human intestinal tract during normal digestion.



The collection of 240 intestinal samples from 15 healthy individuals using the device and subsequent multi-omics analyses identified significant differences between bacteria, phages, host proteins, and metabolites in the intestines versus stool. Certain microbial taxa were differentially enriched, and prophage induction was more prevalent in the intestines than in stool. The host proteome and bile acid profiles varied along the intestines and were highly distinct from those of stool. Correlations between gradients in bile acid concentrations and microbial abundance predicted species that altered the bile acid pool through deconjugation.

Furthermore, microbially conjugated bile acid concentrations exhibited amino acid-dependent trends that were not apparent in the stool. Overall, non-invasive, longitudinal profiling of microorganisms, proteins, and bile acids along the intestinal tract under physiological conditions can help elucidate the roles of the gut microbiome and metabolome in human physiology and disease. *Nature*. 2023 May;617(7961):581-591. doi: 10.1038/s41586-023-05989-7.

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