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New vectors for gene delivery: Human and mouse artificial chromosomes

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Our human artificial chromosomes (HACs) have been generated mainly by a "top-down approach" (engineered creation). HACs with acceptor sites exhibit several characteristics required by an ideal gene delivery vector, including stable episomal maintenance and capacity to carry large genomic loci plus their regulatory elements, thus allowing the physiological regulation of the introduced gene in a manner similar to that of native chromosomes. Mouse artificial chromosomes (MACs) with acceptor sites were also created from a native mouse chromosome. The lessons learned and prospects identified from studies on the construction of HACs and MACs, their ability to drive exogenous gene expression in cultured cells, and transgenic animals. Multiple integration sites were also loaded in HAC/MAC. The recent emergence of stem cell-based tissue engineering has opened up new avenues for gene-and cell-therapies. Possible applications for medical and pharmaceutical use of HACs and MACs are also proposed, e.g., evaluation of function and safety for during and foods, toxicity for chemicals, mechanistic studies of genetic disorders, navigation and monitoring-system for cell differentiation, and model animals for genetic disorders.

The mouse ENCODE project—part of the ENCODE, or ENCyclopedia Of DNA Elements, program—aims to examine the genetic and biochemical processes involved in regulating the mouse and human genomes. Launched by NIH's National Human Genome Research Institute (NHGRI), ENCODE has been building a comprehensive catalog of functional elements in the human and mouse genomes. These elements include the genes that provide instructions to build proteins, non-protein-coding genes, and regulatory elements that control when genes are expressed (turned on and off) in different cells and tissues.ENCODE scientists applied several genomic approaches to 123 different mouse cell types and tissues, and then compared them with the human genome. The results appeared in 4 papers in Nature on November 20, 2014, and several related papers in Science, Proceedings of the National Academy of Sciences, and other journals.The researchers found that, at a general level, gene regulation and other systems important to mammalian biology have many similarities between mice and humans. Specific DNA sequence differences linked to diseases in humans often have counterparts in the mouse genome. Genes whose expression patterns are related in one species also tend to be similarly related in the other species. These findings validate the importance of using mouse models to study certain human diseases.

However, the researchers uncovered many DNA variations and gene expression patterns that are not shared between the species. Understanding these differences enhances the value of the mouse as a model organism. For example, the regulatory elements and activity of many genes of the immune system, metabolic processes, and stress response vary between mice and humans.“In general, the gene regulation machinery and networks are conserved in mouse and human, but the details differ quite a bit,” notes Dr. Michael Snyder of Stanford University, a co-senior author on the main Nature study. “By understanding the differences, we can understand how and when the mouse model can best be used.”“These results provide a wealth of information about how the mouse genome works, and a foundation on which scientists can build to further understand both mouse and human biology,” says NHGRI Director Dr. Eric Green.ENCODE data are freely shared with the biomedical community. The mouse resource has already been used by researchers in about 50 publications to date.