RNA induction of an epigenetic hereditary pathology

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A new study shows that microinjection of RNA molecules into mouse embryos induces a hereditary form of cardiac hypertrophy that is similar to human hypertrophic cardiomyopathy (HCM). The research, published by Cell Press in the June issue of the journal Developmental Cell, may provide a paradigm for clinical cases of familial diseases not readily explained by DNA mutations.

Dr. Minoo Rassoulzadegan from the University of Nice and her colleagues had previously shown that RNA, a molecule that is similar to DNA and important for the process of protein synthesis, can play an unexpected role in passing characteristics on to future generations, even in the absence of DNA mutations affecting those characteristics. This phenomenon is known as hereditary epigenetic determination, or paramutation.

The researchers sought to expand on this earlier work by examining the relevance of paramutation to pathophysiology and disease. They focused on HCM, an important often hereditary heart disease characterized by enlargement of cardiac muscle cells. "There is no clear molecular link between mutations associated with hereditary cardiomyopathies, inheritance of the disease and the abnormal growth of cardiac muscle cells, leading to the suspicion that other, still unknown factors are involved," offers Dr. Rassoulzadegan.

Dr. Rassoulzadegan's group used their method to show that injecting microRNA-1, a known regulator of cardiac development, into one-cell

mouse embryos resulted in mice with substantially enlarged hearts similar to HCM. The injected RNA initiated epigenetic changes in targets such as Cdk9, a gene that regulates cardiac growth. Remarkably, these changes were then inherited both paternally and maternally for three generations. The authors attribute this phenomenon to the transmission of the excess microRNA via sperm.

The authors conclude that hereditary human cardiac problems that do not seem linked to DNA mutations may be caused instead by aberrant RNAs. "These results highlight the diversity of RNA-mediated epigenetic effects. They extend the concept of a mode of variation and heredity, distinct from and complementary to principles of Mendelian genetics, an observation that is potentially significant for both fundamental biology and pathology," says Dr. Rassoulzadegan.

Source: Cell Press

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