Research team discovers genes and disease mechanisms behind a common form of muscular dystrophy

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Continuing a series of groundbreaking discoveries begun in 2010 about the genetic causes of the third most common form of inherited muscular dystrophy, an international team of researchers led by a scientist at Fred Hutchinson Cancer Research Center has identified the genes and proteins that damage muscle cells, as well as the mechanisms that can cause the disease. The findings are online and will be reported in the Jan. 17 print edition of the journal *Developmental Cell*.

The discovery could lead to a biomarker-based test for diagnosing facioscapulohumeral muscular dystrophy (FSHD), and the findings have implications for developing future treatments as well as for cancer immunotherapies in general.

The work establishes a viable roadmap for how the expression of the DUX4 gene can cause FSHD. Whether this is the sole cause of FSHD is not known; however, the latest findings "are about as strong of evidence as you can get" of the genetic link, said corresponding author Stephen Tapscott, M.D., Ph.D., a member of the Hutchinson Center's Human Biology Division.

Tapscott and colleagues sought answers to the questions about what the DUX4 protein does both normally in the body and in the FSHD disease process. In the latest study, they identified that the DUX4 protein regulates many genes that are normally expressed in the male germ line but are abnormally expressed in FSHD muscle. Germ line cells are inherited from parents and passed down to their offspring.

"This study is a significant step forward by solidifying that the DUX4 transcription factor causes this disease, while offering a number of viable mechanisms for why the muscle is damaged," Tapscott said. Transcription factors are tools that cells use to control gene expression. Genes that are "turned on" in the body are "transcribed," or translated, into proteins.

Now that scientists know that targets for DUX4 are expressed in skeletal muscle, an antibody- or RNA-based test could be developed to diagnose FSHD by examining muscle tissue from a biopsy, Tapscott said. Such biomarker-based tests also could be used to determine how well new treatments are working to suppress FSHD.

The study also discovered that DUX4 regulates cancer/testis antigens. Cancer/testis antigens are encoded by genes that are normally expressed only in the human germ line, but are also abnormally expressed in various tumor types, including melanoma and carcinomas of the bladder, lung and liver.

"This knowledge now gives us a way to manipulate the expression of cancer/ testis antigens, potentially opening the opportunity to use these antigens in a cancer vaccine," Tapscott said.

Two papers published in 2010 by the same group of researchers established the genetic basis for showing that expression of DUX4 was necessary for the disease. The previous research also identified the RNA in the FSHD muscles and showed that it was normally expressed in the germ line, which led to the hypothesis that the lack of an efficient developmental repression of this RNA caused the disease.

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