A new genetic switching element

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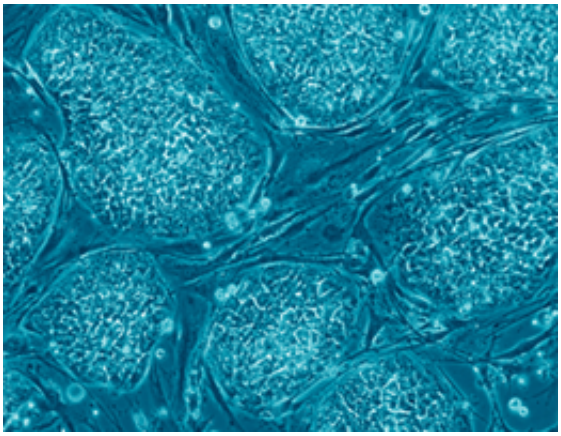

Stem cells. Credit: Nissim Benvenisty - Wikipedia

Slight modifications in their genome sequences play a crucial role in the conversion of pluripotent stem cells into various differentiated cell types. A team at Ludwig-Maximilians-Universitaet (LMU) in Munich has now identified the factor responsible for one class of modification.

Every cell contains stored hereditary information, encoded in the sequence of nucleobases that make up its DNA. However, in any given cell type, only a fraction of this information is actually used. Which genes are activated and which are turned off is in part determined by a second tier of information which is superimposed on the nucleotide sequences that provide the blueprints for protein synthesis. This so-called epigenetic level of control is based on the localized, and in principle reversible, attachment of simple chemical tags to specific

nucleotides in the genome. This system plays a major role in the regulation of gene activity, and enables the selective expression of different functions in differentiated cell types.

This explains why such DNA modifications play a major role in the differentiation of stem cells. "Several unusual nucleobases have been found in the genomes of stem cells, which are produced by targeted chemical modification of the known building blocks of DNA. These 'atypical' bases are thought to be important in determining what types of differentiated cells can be derived from a given stem cell line," says Professor Thomas Carell from the Department of Chemistry at LMU. All of the unconventional bases so far discovered are derived from the same standard base – cytosine. Furthermore, Carell and his team have shown in earlier work that so-called Tet enzymes are always involved in their synthesis.

Base oxidation regulates gene activity

In cooperation with colleagues at LMU, as well as researchers based in Berlin, Basel and Utrecht, Carell and his group have now shown, for the first time, that a standard base other than cytosine is also modified in embryonic stem cells of mice. Moreover, Tet is at work here too. "During the development of specialized tissues from stem cells, enzymes belonging to the Tet family also oxidize the thymidine base, as we have now shown with the aid of highly sensitive analytical methods based on mass spectrometry. The product of the reaction, hydroxymethyluracil, was previously – and as it now turns out, erroneously – thought to be synthesized by a different pathway," Carell explains.

The precise function of hydroxymethyluracil remains unclear. However, using an innovative method for the identification of factors capable of binding to and "reading" the chemical tags that characterize unconventional DNA bases, Carell and colleagues have shown that stem

cells contain specific proteins that recognize hydroxymethyluracil, and could therefore contribute to the regulation of gene activity in these cells. "We hope that these new insights will make it possible to modulate the differentiation of stem cells – causing them to generate cells of a particular type," says Carell. "It would be wonderful if we were one day able to generate whole organs starting from differentiated cells produced, on demand, by stem cell populations."

More information: www.nature.com/nchembio/journa … l/nchembio.1532.html

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