

Press Release

Jumonjd3: a key for unlocking neuronal stem cell fate

A novel role for the protein, *Jumonjd3*, as an epigenetic modulator in the neuronal differentiation of embryonic stem cells, has recently been uncovered at the IFOM-IEO Campus in Milan – a step forward in the understanding of cellular reprogramming and in the development of innovative cancer therapies.

A protein named **Jumonjd3** has been identified by a team of scientists at the **IFOM-IEO Campus** in Milan, as the molecular key required for starting up the differentiation process and for issuing neuronal “identity cards” to embryonic stem cells.

The research, conducted by a team of scientists led by Giuseppe Testa, Director of the *Stem Cell Epigenetics Programme* at the **Department of Experimental Oncology at IEO**, focuses on a particular group of ‘**bivalent**’ genes that, during embryonic stem cell differentiation, are either activated or repressed, bestowing stem cells with a neuronal identity

Epigenetic modifications and cellular identity

The cells that make up our body all share the same set of approximately 30,000 genes, inherited from the single cell (i.e., the fertilized egg) that started everything off. However, during **functional differentiation**, when cells assume their **identity** (e.g., they become a neuronal, blood or liver cell) in order to carry out a **specific role** in the body, only a particular set of genes within the cell are activated, while the others are **silenced**. This selective control of gene expression occurs at the **epigenetic level** (from the Greek *epi- “in addition to-” genes*), through chemical modifications that control gene expression by activating or repressing specific genes without altering the underlying DNA sequence. An important epigenetic mechanism controlling the functional differentiation of embryonic stem cells is histone methylation. Histones are a family of proteins that play a critical role in ordering DNA filaments within chromatin. Histones form the protein core of **nucleosomes**, repeating units in chromatin, around which DNA is wrapped and compacted. Like all proteins, histones are made up of amino acids arranged in a linear chain: one end of this chain, known as the **amino-terminal tail**, protrudes from the nucleosome core and is, therefore, freely available to undergo epigenetic modifications. Specific protein complexes control the methylation of this tail during cellular differentiation, leading to chromatin remodeling and the activation/repression of specific target genes.

In particular, the methylation of two amino acids in histone H3, **lysine 4 and lysine 27**, has opposing effects on gene expression in stem cells: if lysine 4 is methylated the gene is **expressed**, if lysine 27 is methylated the gene is **silenced**.

A breakdown in the methylation machinery can significantly affect the identity of cells and may cause malformations in embryos or, in adults, **a number of pathological conditions, in particular, cancers**. It is not surprising, therefore, that in the so-called **big killers** (cancer of the colon, lung, breast and prostate), abnormal epigenetic modifications (i.e., epimutations) have been detected, such as the erroneous repression of genes by methylation of histone H3 on lysine 27.

For decades, histone methylation was considered as an **irreversible chemical event**; however, recently it has been observed that **demethylation** (i.e., the removal of methyl groups) of specific genes can occur under certain conditions during cellular differentiation. This process is, at present, poorly understood, but the scientific community is working on different fronts to identify proteins involved in demethylation. An important contribution to our understanding of demethylation has recently been made by researchers at the **IFOM-IEO Campus** in Milan: a centre of excellence founded from **IFOM** (FIRC Institute of Molecular Oncology) and **IEO** (European Institute of Oncology) and amongst the most prestigious centres, at the international level, working on epigenetic research.

Jumonjd3 and the dynamic identity of neuronal cells

Research conducted by **Giuseppe Testa**, Director of the *Stem Cell Epigenetics Programme* at the Department of Experimental Oncology at IEO, in collaboration with Gioacchino Natoli, Director of the *Transcriptional Control in Inflammation and Cancer Laboratory* at the same Institute, identified **Jumonjd3** as an enzyme that controls neuronal differentiation of stem cells by removing silencing signals from genes that are essential for neurogenesis.

In embryonic stem cells, a group of genes, defined as '**bivalent**', are characterized by their association with Histone H3, methylated on two residues, **lysine 4 and lysine 27**. Paradoxically, methylation of these two residues has opposing effects on gene expression. During the differentiation of the neuronal lineage, these genes **lose their bivalent character** by **demethylation** of one of the two lysine residues. This leads to either the complete activation or complete silencing of particular genes that grant stem cells a **new neuronal identity**.

The enzyme responsible for the demethylation of lysine 27 during neuronal differentiation has been identified by Giuseppe Testa and colleagues as **Jumonjd3** (Jumonji in Japanese means *cross-shaped*).

"Our characterization of the role of Jumonjd3 in neuronal differentiation supports the notion that epigenetic modifications, which regulate cell fate and identity, represent a **dynamic and plastic mechanism** for controlling gene expression." explained Testa "It is plausible that Jumonjd3 will one day represent an important target in the exploitation of **cellular programming and reprogramming** for therapeutic purposes". This research is a significant step forward in our understanding of the intricate mechanisms that regulate stem cell functions. In the long term, Jumonjd3 could constitute a **promising target in the reprogramming of differentiated cells** and in the **development of antineoplastic therapies that counteract the abnormal differentiation processes at the route of tumorigenesis**.

Giuseppe Testa and his research group have performed *in vitro* and *in vivo* experiments on cells from model organisms using innovative experimental methods based on **chromatin immunoprecipitation** (a technique that "immortalizes" the interactions between specific proteins and regions of the genome in a particular instance in the cell's life).

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