Scientific Newsletter

Interdisciplinary Research Institute of Grenoble

SPRING 2023

Study of a fly protein point out towards a non-catalytic role for the RNA methyltransferase PCIF1 in gene expression

In living organisms, gene expression is a complex process that results in the production of proteins from the genome in a time- and space-regulated manner. This expression is strictly dependent on the synthesis of messenger RNAs transcripts from the DNA molecule and their subsequent translation into proteins by the ribosomes. As they are synthesized, mRNAs undergo chemical modifications that ensure their stability, their delivery to ribosomes and eventually their translation into proteins. These modifications include the addition of a cap at the 5' end and polyadenosines tail at the 3' end, as well as the addition of methyl groups on various nucleotides. These numerous modifications provide an additional level of information for the control of protein production and collectively form the epi-transcriptome.

Researchers at IRIG, in collaboration with the University of Geneva, focused on a RNA mammalian methyltransferase, the PCIF1 protein (homologous to the Drosophila Pcif1 protein), which adds an extra methyl group to m^6A (m^6 adenosine) to form m^6Am when the first transcribed nucleotide is an adenosine. In mice, mutation of PCIF1 encoding gene causes deregulation of the expression of a set of genes and a reduced body weight. During evolution, this protein naturally lost its catalytic activity in Drosophila where Pcif1 is, like its human counterpart, expressed in the nucleus and associated with the C-terminal domain of RNA polymerase (RNA Pol II). The work of the scientists shows that mutation of *Pcif1* gene in Drosophila results in a deregulation of the expression of a set of genes, reduced body weight and a significant drop in fertility which indicates an important role for this protein in the physiology of the organism. In agreement with these observations, the Pcif1 protein is distributed all along the **polytene chromosomes** at the level of active transcription sites and interferes with chromatin-dependent gene expression regulation. This protein binds to the phosphorylated form of serine 5 of RNA polymerase II (Figure) and may directly modulate its activity or promote the recruitment of chromatin components. These results suggest a similar contribution of PCIF1 to the fine regulation of RNA polymerase II activity in mammals, in addition to its mRNA methylation activity, whose role in mRNA translation efficiency is actively studied but still controversial.

This study demonstrates the importance to not restrict the function of enzymes to their sole catalytic role in the living world and the interest of thoroughly examining the evolution of proteins in eukaryotes in order to discover unsuspected or hidden mechanisms of action.

This work has been funded by the LabEX GRAL, ANR-10-LABX-49-01 and IDEX PhD international grant (to GF) financed within the University of Grenoble Alpes graduate school (Ecoles Universitaires de Recherche) CBH-EUR-GS (ANR-17-EURE-0003) and the Région Rhône-Alpes (international program).

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BGE
Biosciences and bioengineering for health

The lack of **catalytic of Pcif1 in Drosophila reveals a new mechanism of gene expression regulation.**

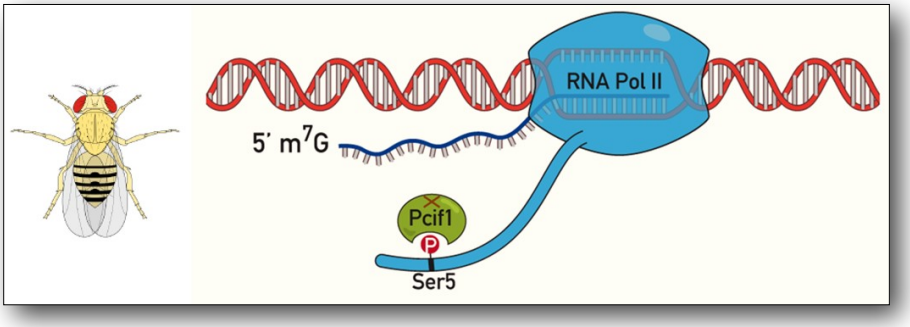

Figure A: The mammalian PCIF1 catalyses methylation (m^6Am) of the first transcribed nucleotide of a messenger RNA, when it is an adenosine, however its fly PCIF1 counterpart is naturally catalytically-dead. The fly Pcif1 expressed in the nucleus and binds the phosphorylated C-terminal domain (CTD) of RNA Pol II (at the level of phosphorylated serine 5).

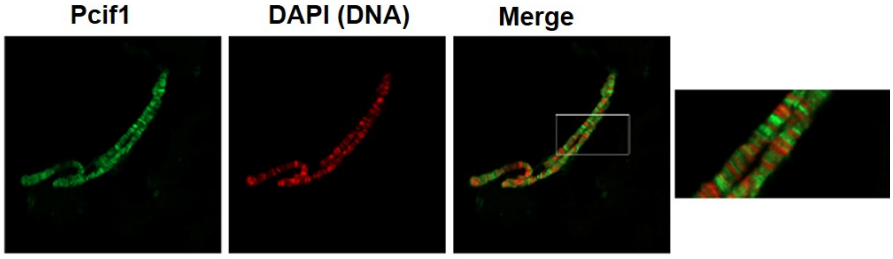

Figure B: Immunofluorescence analysis with anti-Pcif1 antibodies revealed the presence of the Pcif1 protein (in green) along the chromosome at transcriptionally active euchromatin sites (*i.e.* excluded from DAPI dense staining, in red).
Based on work described in Pandey *et al.* 2020; Franco *et al.* 2023.

Polytene chromosomes *result from a succession of chromatid duplications that remain associated without concomitant cell division. They are made up of several hundred or thousands of chromatids. Regions of condensed chromatin can be observed (called heterochromatin, in red on the figure), and less condensed regions of chromatin (called euchromatin) which correspond to sites of active transcription of DNA into RNA..*

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The catalytic-dead Pcif1 regulates gene expression and fertility in Drosophila.
RNA 2023

Pandey RR, Delfino E, Homolka D, Roithova A, Chen KM, Li L, Franco G, Vågbø CB, Taillebourg E, Fauvarque MO and Pillai RS
The mammalian cap-specific m^6Am RNA methyltransferase PCIF1 regulates transcript levels in mouse tissues.
Cell Report 2020

NLRP7 protein disguises placental cancer from the mother

Placental cancer, or gestational choriocarcinoma, can unfortunately cause maternal death even several years after the pregnancy. Researchers at IRIG are studying the behavior of the NLRP7 protein involved in inflammatory processes suspected in the development of this cancer. In 2021, they had shown that the overexpression of NLRP7 in placental cancer cells contributed to their metastasis to other organs, such as the liver, the lung or the brain.

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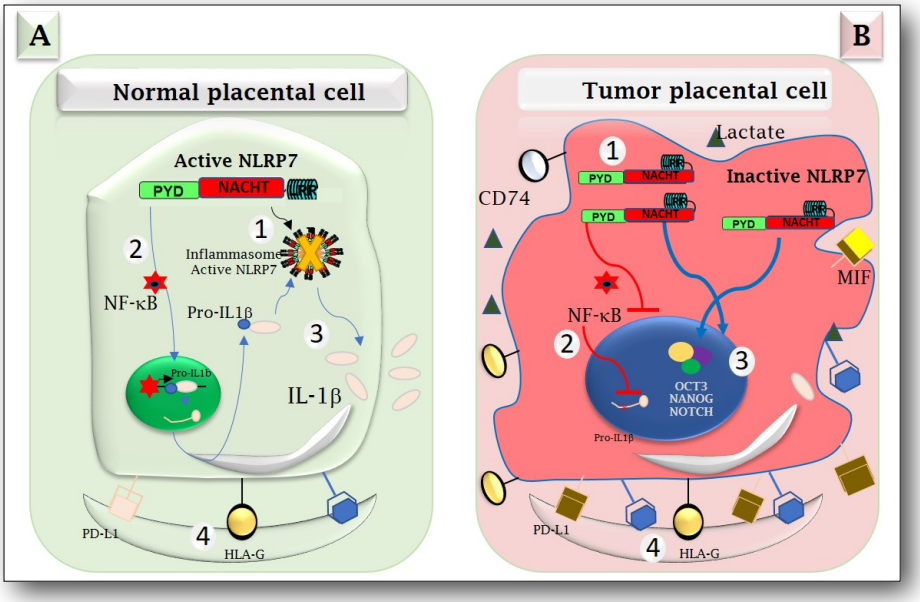
Continuing this work, researchers at IRIG first compared the mechanisms of NLRP7 protein function in a normal placenta cell and in a cancer placenta cell. The normal cell was collected from the placenta of a pregnant woman, and the tumor cell was recovered from a patient who had died of choriocarcinoma.
In the normal cell (Figure A), the NLRP7 protein functions in a mode dependent upon its inflammatory machinery called, inflammasome, which allows the production of pro-inflammatory cytokines, such as interleukin-1β (IL-1β).
In the tumor cell (Figure B), the researchers showed that overexpression of NLRP7 blocks the activation of the NF-κB protein, that allows to produce IL-1β precursor, the pro-IL-1β, wich drives NLRP7 to function in an inflammasome independant pathway.

In addition, the researchers demonstrated that NLRP7 increases tumor cell survival and camouflage. Finally, the researchers injected choriocarcinoma tumor cells expressing or not the *Nlrp7* gene into the tail of a mouse. The results showed that cells overexpressing *Nlrp7* were less exposed to the mouse's immune defense system, and that mice injected with these cells developed larger tumors and had more metastases. Analysis of the tumors and their environments confirmed the decrease in the activation of the host immune system.

These studies demonstrated that NLRP7 contributes to the growth and tumorigenesis of placental cancer. NLRP7 contributes to the development of a mechanism that impedes tumor clearance by the maternal immune system.
These findings suggest that the targeting of NLRP7 may pave the way for new therapies to be proposed to patients with choriocarcinoma, in particular, those who develop resistance to conventional treatments.



A summary model illustrating the mechanism by which NLRP7 contributes to choriocarcinoma tumorigenesis.

Figure A: In non-tumor trophoblast cells, NLRP7 is expressed at normal levels and functions in an inflammasome-dependent manner. In these cells, NLRP7 activates the NF-κB pathway and induces its translocation to the nucleus, which in turn induces the transcription of Pro-IL-1β that matures into IL-1β. NLRP7 also regulates the expression of HLA-G and PD-L1, contributing to trophoblast tolerance by the maternal immune system. All these events contribute to the safe progression of the pregnancy.

Figure B: In tumor trophoblast cells, NLRP7 is overexpressed and functions in an inflammasome-independent manner. It inhibits IL-1β production by decreasing NF-kB activation. NLRP7 also mediates the overexpression of HLA-G, PD-L1 and OCT3, NANOG and NOTCH proteins. These events increase the maternal immune tolerance of tumor cells, which creates a favorable anti-inflammatory environment that contributes to tumor growth.

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NLRP7 enhances choriocarcinoma cell survival and camouflage in an inflammasome independent pathway.
Cells 2023

Watch your steps while growing nanowires

The development of semiconductor nanostructures has been achieved through a good control of their fabrication, for instance by Molecular Beam Epitaxy (MBE). For a long time, this technique has been limited to the growth of planar structures such as quantum wells, inducing a spatial confinement of charge carriers in the perpendicular direction. New challenges, such as the realization of single-photon emitters for quantum communications, require a stronger confinement in two or three directions, obtained by making nanowires and quantum dots.

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Joël Cibert
Institut Néel
NPSC
NanoPhysics and SemiConductors

The growth of nanowires is usually seeded by a liquid droplet of a few nanometers, which determines the diameter of the nanowire. During the growth, quantum dots can be inserted by changing abruptly the composition of the molecular beam. This "Vapor-Liquid-Solid" mechanism combines a vapor phase in the beam, a liquid phase in the droplet, and a solid phase in the nanowire. At the seed-nanowire interface, the growth was supposed to take place through the nucleation of a one-monolayer step and its propagation along this interface. For years, this was a mere assumption. The Nanomax setup at Centre for Nanoscience and Nanotechnology (C2N) Palaiseau, France, now allows to observe this process *in-situ* in a modified electron microscope.

Researchers at IRIG and at Neel Institute (Nano Physic and Semiconductors NPSC, Grenoble), are interested in II-VI semiconductors combining a metal (Zn or Cd column II of the Mendeleev table) and a chalcogen (Se or Te column VI). These materials are particularly interesting as active optical elements, for light emission or photovoltaics. II-VI nanowires can be grown with a gold seed which is solid and crystalline instead of liquid: this is the "Vapor-Solid-Solid" growth, which is expected to provide sharper interfaces when inserting a quantum dot.
Observing the growth of ZnTe nanowires at Nanomax revealed two original aspects: the role of the lattice mismatch at the nanowire-seed interface, and a self-regulation of the step dynamics.

Gold and ZnTe crystals feature the same lattice, but the ZnTe unit cell is 3/2 larger than that of gold. When the gold monolayer located at the interface is progressively replaced by a ZnTe monolayer, a strong mismatch strain appears at the step, which creates a barrier against the formation of such step.
Alternatively, a different step configuration, made of 2 ZnTe monolayers facing 3 gold monolayers, shows practically no mismatch making this configuration more favorable. And indeed, the Nanomax investigation revealed this growth proceeds for liquid nanoparticles (Fig. 1 and movie 1). And when nanoparticle is liquid the propagation is made both with one or two monolayers steps (movie 2).

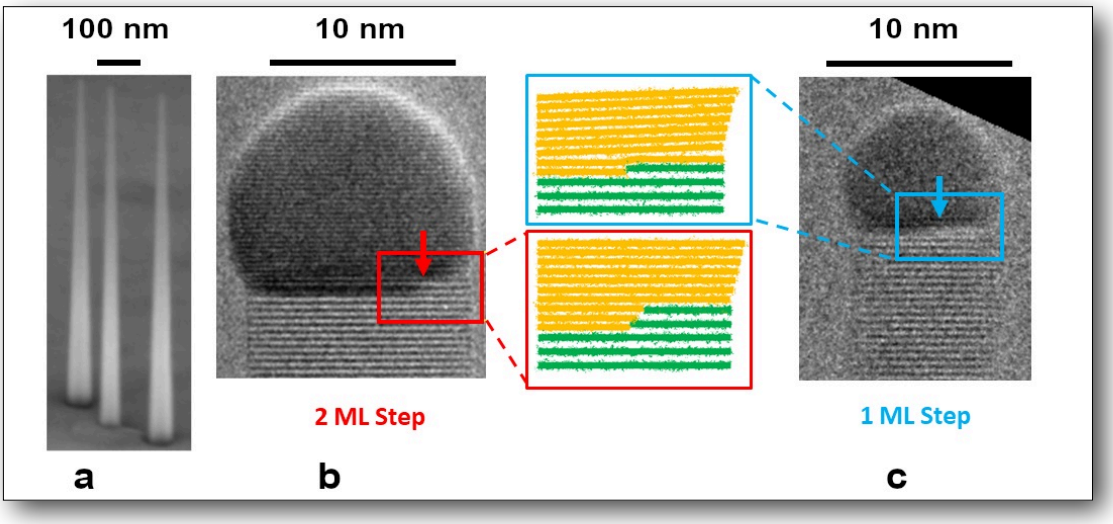
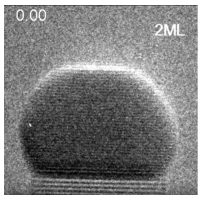
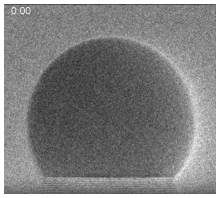


Figure: (a) ZnTe nanowires grown in MBE cluster; (b) Nanomax image showing the gold seed at the top of the ZnTe nanowire, with a two-monolayer step at the interface; the step (indicated by the arrow) propagates from right to left; (c) idem, with a one-monolayer step. The schemes in-between display the Au atomic planes (in yellow) and the ZnTe planes (in green) for the two configurations.



Movie 1



Movie 2

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Regulated dynamics with two-monolayer steps in Vapor-Solid-Solid Growth of nanowires.
ACS Nano 2022

Medical implants: Autonomous tomorrow?

Implantable medical devices benefit from the improved autonomy of cells and batteries. However, their autonomy remains unsatisfactory for patient comfort. For instance, the battery of an artificial heart must be recharged every 24 hours! An ideal solution would be for the medical device to use the same energy source as the organ it replaces, *i.e.* glucose and blood oxygen. Thus, the conversion of chemical energy into electricity to power the medical device can be achieved through a fuel cell. However the latter was not originally designed to be implanted in a living organism, since glucose and oxygen are not the most suitable reagents for its operation.

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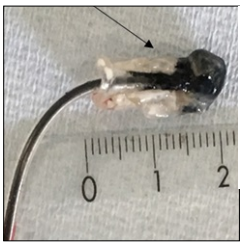
Therefore, the following two locks must be taken into account:

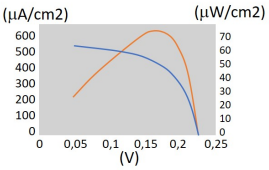
i. In order to be supplied with glucose and oxygen, the electrodes of the battery are necessarily in contact with the body; they must therefore be fully biocompatible to avoid any inflammatory reaction.

ii. As each electrode is in contact with the biological medium, including the two reactants, glucose and oxygen, it is necessary that the catalysts used for the conversion of chemical energy into electricity are highly selective. To date, only enzymes, which are not very stable, have the necessary selectivity to design implantable fuel cells.

Researchers at Irig, working on graphene derivatives, have developed platinum-free chemical catalysts that are highly selective for oxygen reduction. In **collaboration** they improved the efficiency of the catalysts under physiological conditions. These graphene-based catalysts have been shown to be biocompatible, opening the way to proof of concept in animals. The fabrication of the electrodes has been optimized in order to control their porosity for a good diffusion of the reagents, in particular by using 3D printing techniques. Finally, new membranes have been developed to avoid the fouling of electrodes by cells (biofouling), and thus avoid the loss of performance of implantable fuel cells.



Fuel cell after 5 months of implantation



Polarization curve of the fuel cell after explantation (blue: surface current - left axis, orange: surface power - right axis).

These new implantable fuel cells were first tested *in vitro* for more than a year in order to demonstrate that they retain their electrochemical performance and biocompatibility. They were then implanted in rats for more than 6 months. The batteries remained operational and intact during this long implantation period. Another remarkable result: they did not cause rejection or inflammatory reactions.

These studies thus made it possible to remove important obstacles to the development of bioimplantable fuel cells. Even if important challenges still exist, in particular concerning the glucose oxidation catalysts, they open the way to the development of more efficient and above all energy autonomous implanted medical devices.

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RSC Adv. 2023

Collaboration
TIMC *(Recherche Translationnelle et Innovation en Médecine et Complexité): laboratory specialized in implantable technologies*
IC2MP *(Recherche Translationnelle et Innovation en Médecine et Complexité) University of Grenoble Alpes-CNRS-INSERM, Poitiers): develops catalysts based on gold nanoparticles, selective for glucose oxidation*
LGP2 *((Laboratory of Process Engineering for Biorefinery, Bio-based Materials and Functional Printing, Grenoble): produces electrodes by printing or lithography processes*
BIOPIC *(Normandy) company sells implanted sensors for real-time monitoring of farm animal health.*

The enzyme laccase to detoxify food aflatoxins

Aflatoxins are known to be highly toxic as they can have serious health consequences for humans and animals. They are toxic fungal metabolites that can contaminate a wide range of food and feed crops, including peanuts, corn and tree nuts. They are produced by certain species of Aspergillus fungi which grow on crops before or after harvest, especially under warm, humid conditions. Exposure to aflatoxins has been associated with an increased risk of various cancers, including lung and digestive cancers.

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Prevention of aflatoxin contamination is a major challenge for the food and feed industries. Various strategies are used to reduce their occurrence and understanding the mode of action of laccase is essential.

To evaluate the ability of this enzyme to detoxify aflatoxins, researchers at IRIG conducted a study based on combined experimental and theoretical approaches. First, *in vitro* experiments showed that laccase was able to efficiently oxidize aflatoxins, leading to their detoxification. Computer simulations were then carried out to study the mechanisms underlying the detoxification process, notably using the **BigDFT** code. The simulations confirmed that laccase was able to bind to aflatoxins and oxidize them through a radical-based mechanism.

BigDFT *is a free software for physicists or chemists, whose main program allows to calculate the total energy and the electronic structure of systems, within density functional theory (DFT) and a wavelet basis.*

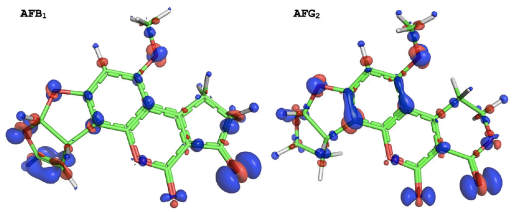

Figure: indication of the oxidation sensitive areas for two different configurations of the aflatoxin molecule by showing the so-called Fukui isosurfaces.

The results of this study suggest that laccase may be a promising enzyme for the detoxification of aflatoxins. Further research will be needed to explore potential applications and deploy laccase-based detoxification strategies in the food industry.

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Scientific report 2023

Editing histones to explore epigenetic regulation of plant development

Eukaryotic DNA, by associating with histones, is organized into a structure named chromatin. On this chromatin, the so-called epigenetic marks allow precise and dynamic control of gene expression, which is necessary for the proper deployment of developmental programs. Among these marks, the post-translational modifications carried by histones have thus far been studied using mutants for the enzymes that catalyze them. This strategy has led to significant advances in the field of epigenetics. However, the multiple and redundant functions of the studied enzymes have prevented depicting the precise role of histone residues and the marks they carry.

Contact: Christel Carles
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Cell & Plant Physiology Laboratory

Collaboration
Institute of Plant Molecular Biology (IBMP) - CNRS in Strasbourg, and the Robert H. Smith Institute of Plant Sciences & Genetics in Agriculture - University of Jerusalem.

Scientists at IRIG [**collaboration**] have sought to decipher the true function of lysine 27 on histone H3 (H3K27) in more detail by developing a novel approach, published in *New Phytologist*.

This approach consists of having the model plant *Arabidopsis thaliana* express a histone H3 variant carrying an alanine instead of a lysine at position 27, inducing a drastic decrease in the level of methylation on H3K27. A detailed phenotypic analysis revealed strong developmental effects in the corresponding lines, some reminiscent of observations already made in enzymatic mutants, others singular and never demonstrated before. In addition to early flowering, curled leaves and accelerated proliferation of "callus" from undifferentiated cells, the lines obtained show shortened stems with altered organization into cell types. Transcriptomic and metabolomic analyses indicate that the latter phenotype is the result of a deregulation of metabolic fluxes in the phenylpropanoid and lignin biosynthetic pathway.

With this work, the scientists shed new light on the different roles played by lysine 27 of histone H3 in plants, including the regulation of key metabolic pathways involved in lignin composition and the control of stem elongation. This approach, applied to other histone protein residues or in other plant species, shall reveal new functions in the regulation of gene expression in development and response to environmental signals.

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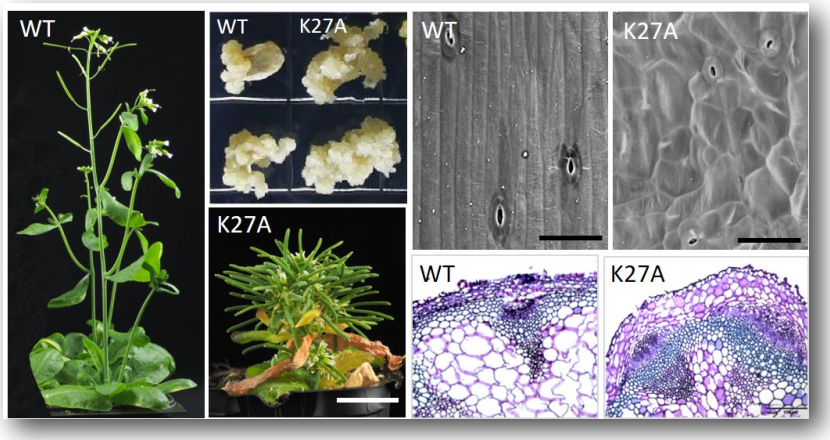
Lysine 27 of histone H3.3 is a fine modulator of developmental gene expression and stands as an epigenetic checkpoint for lignin biosynthesis in Arabidopsis.
New Phytologist 2023



Arabidopsis plants expressing a modified form of histone H3 (K27A substitution of lysine 27 to alanine) show several morphological differences from control plants expressing an unmodified histone H3 (WT): early flowering and short stem, better callus proliferation, cell type defects on the epidermis and in the lower layers of the stem.

Spintronic memristor based neural network

Convolutional neural networks (CNN) are efficient for certain tasks such as image or text recognition. However, the classical design of a computer in which the processor and the memory are physically separated is not compatible with a neural network. Indeed, the calculations requiring that the synapses exchange frequently between the neurons the information stored in the memory (we speak of synaptic weight) that causes a considerable slowdown. Researchers at IRIG have therefore used spintronic devices that allow a parallel implementation of the networks in which the calculation and storage are integrated in the same block.

Contact: Guillaume Prenat
SPINTEC
Spintronics and Component Technology

Researchers have developed electronic memories called memristors whose resistance changes continuously as a function of applied current. In a memory architecture called "crossbar", the memristors code the synaptic weight as an electrical resistance in order to perform calculations with analog currents that will be converted into digital values. The goal is to realize a convolutional neural network based on memristors which keeps the same performances while minimizing the complexity and without additional hardware cost. However, as the manufacturing process of these spintronic devices is recent, the accuracy of the computation still needs to be made reliable. Moreover, the synaptic weights can only take two binary states which makes it difficult to access different resistance levels in order to mimic a synapse.

To mitigate these issues, the researchers tested an architecture using two concepts. The first one is an ensemble network, according to the "wisdom of crowds" concept, where the global network is replaced by several smaller, less accurate but much simpler networks, which are trained with different samples extracted from the same data set. The results obtained by these networks are then compared to obtain a decision, the accuracy of which is comparable with that of a single network.

The second concept is a binary type network in which the synaptic weights take only two states, contrary to the classical network whose weights vary continuously.

Thanks to these two concepts, spintronic devices allow calculations with almost no loss of precision.

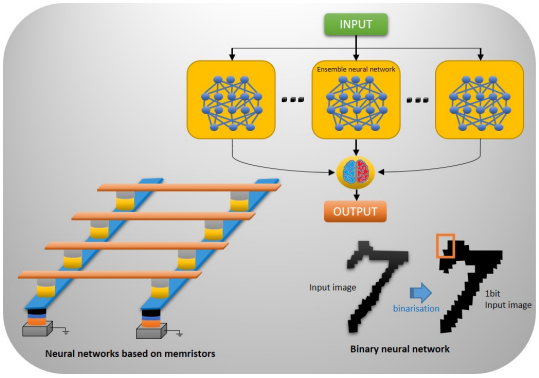


Figure: Neural networks based on spintronic devices (left) combinated with Ensemble neural netwok (up) and Binary neural network (right).

This solution was evaluated on different datasets for image recognition. The architecture of the ensemble network allowed an optimization of the hardware cost, as the number of neurons is reduced by 92% and the number of synapses by 95%, and this with an accuracy similar to that of a single equivalent convolutional network. In addition, a 95% reduction in the number of clock cycles and 97% reduction in the number of memory accesses was observed. And finally, the use of spin-orbit coupled devices allows for a further three orders of magnitude reduction in power consumption due to reduced computational currents.

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Spintronic memristor based binarized ensemble convolutional neural network architectures.
IEEE Transactions on Computer-Aided Design of Integrated Circuits and Systems 2022

Convolutional Neural network (CNN) is a class of artificial neural network most commonly applied to analyze visual imagery.
Memristor is a non-linear two-terminal electrical component relating electric charge and magnetic flux linkage.

The biogenesis of iron-sulfur centers, a very ancient origin

Fe-S clusters are protein cofactors essential to life. They result from the assembly between ferrous and/or ferric ions and sulfide ions. Present in proteins, they are involved in many essential cellular processes. It has been proposed for a long time in the field of Fe-S assembly that in an oxygen-free atmosphere, rich in iron and sulfur, Fe-S were formed spontaneously. With the appearance of a high concentration of oxygen on Earth, 2.4 billion years ago, the mechanisms of Fe-S cluster formation changed, in particular because of the oxidation of bioavailable iron and the presence of reactive oxygen species. Thus, organisms adapted by developing specific protein systems for Fe-S cluster biosynthesis (**NIF**, **ISC** and **SUF**), allowing Fe-S clusters to be synthesized in a controlled manner.

However, a recent study proposes a different scenario. Teams of researchers at IRIG and Institut Pasteur of Paris have combined their expertise to study the evolutionary history of the biogenesis machinery of Fe-S clusters. Using a genomic approach, by analyzing more than 10,000 genomes, the researchers identified two new machineries named **MIS** and **SMS** present in many prokaryotes and dating back to the last universal common ancestor (LUCA). The scientists have characterized at the molecular level by biochemical approaches one of these two machineries (SMS), showing that it is indeed a system involved in the assembly of Fe-S clusters. Very ancient, these MIS and SMS machineries have then evolved in bacteria to give rise to the three machineries NIF, ISC and SUF.

This work shows that the assembly machinery of Fe-S clusters did not appear with oxygenation on Earth but well before, and opens new perspectives for the understanding of the very first metabolisms related to the origin of life.

***NIF**: Nitrogen Fixation*
***ISC**: Iron Sulfur Cluster*
***SUF**: SUIFur*
***SMS**: Suf-like Minimal System*
***MIS**: Minimal Iron Sulfur*

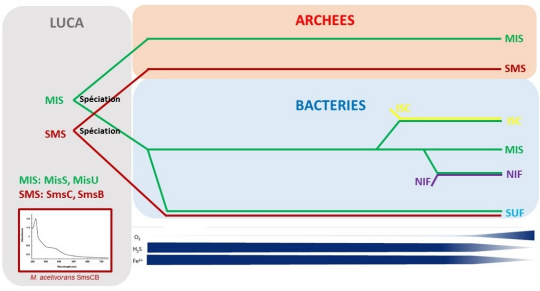

Figure: Scenario for the origin and evolution of the biogenesis machinery of iron-sulfur clusters with reconstruction of ancestral systems and main evolutionary events.

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An early origin of iron-sulfur cluster biosynthesis machineries before Earth oxygenation.
Nature Ecology & Evolution 2022

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ESCRT-III membrane neck cleavage mechanism revealed

Within the protein family, ESCRT-III members are present in evolution from prokaryotes to metazoans. They polymerize on membranes in order to remodel them, often to the point of membrane fission co-catalyzed by the activity of the ATPase VPS4. Various pathologies such as cancer and neuronal deficiencies are linked to the dysfunction of the ESCRT machinery. Notably ESCRT-III and VPS4 have been associated with late steps in membrane cleavage. It is therefore important to study the structure of the ESCRT machinery within a membrane context in order to provide insight into its membrane remodeling and cleavage activity during membrane repair, budding of enveloped viruses, and **cytokinesis** among others.

Contact: Winfried Weissenhorn
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institut de Biologie Structurale

Researchers at IRIG (**collaboration** with Curie Institute, Paris and University of Groningen, Groningen, Netherlands) provide first high resolution cryoEM structures of ESCRT-III filaments composed of **CHMP2A** and **CHMP3** forming membrane-coated tubular structures *in vitro* that resemble ESCRT-III filament architectures at virus or vesicle budding sites or the cytokinetic midbody.

The structures (3.3 Å and 3.6 Å) provide molecular details of helical filament polymerization, membrane interaction and support a model that predicts processive filament sliding upon remodeling by VPS4.

Moreover, single molecule studies confirmed that the ESCRT-III polymers are constricted and cleaved by VPS4 *in vitro*, suggesting that they constitute a minimal machinery that can cleave membrane necks via membrane fission.

ESCRT = Endosomal Sorting Complex Required for Transport is a highly conserved cellular membrane remodeling machinery, consisting of five cytosolic protein complexes, including ESCRT-III and VPS4.

Citokinesis = division of the cytoplasm in the phases of meiosis and mitosis, to separate daughter cells.

CHMP2A = the charged multivesicular body protein 2a is encoded by the gene *CHMP2A*.

CHMP3 = the charged multivesicular body protein 3 is encoded by the gene *VPS24*.

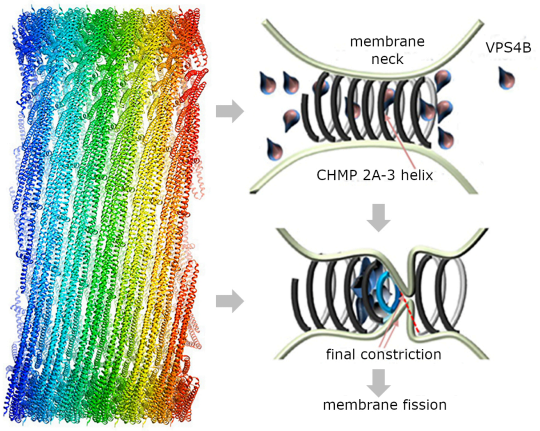

Figure: Model of membrane constriction by ESCRT-III. On the left, atomic model of ESCRT-III filaments composed of a heterodimer of CHMP2A and CHMP3. The outer surface of the filaments interacts with membranes in a manner similar to the topology of membrane collars as shown in the diagram (right). VPS4 tightens the filaments that can cleave membrane necks via membrane fission.

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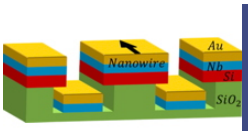

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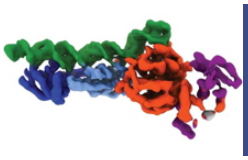

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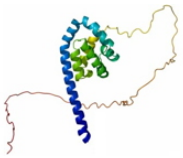

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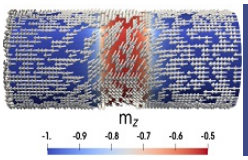

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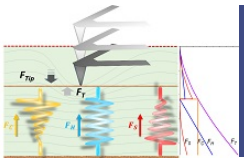

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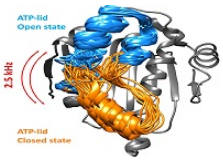

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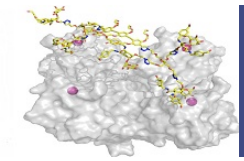

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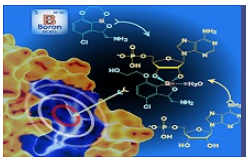

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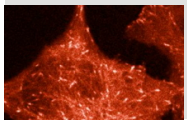

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