SIMPOSIO INTERNACIONAL "CÁNCER, DIABETES Y OBESIDAD: UNA OPORTUNIDAD PARA LA GLICOCIENCIA"

CONACYT
Consejo Nacional de Ciencia y Tecnología

Centro de Investigación en Dinámica Celular

Universidad Autónoma del Estado de Morelos

COMITÉ ORGANIZADOR

Dr. Iván Martínez Duncker Ramírez
Dr. Arturo Edgar Zenteno Galindo

LA REALIZACIÓN DE ESTE EVENTO FUE POSIBLE GRACIAS AL APOYO FINANCIERO RECIBIDO POR PARTE DEL CONSEJO NACIONAL DE CIENCIA Y TECNOLOGÍA A TRAVÉS DE LA RED TEMÁTICA GLICOCIENCIA EN SALUD 270918.

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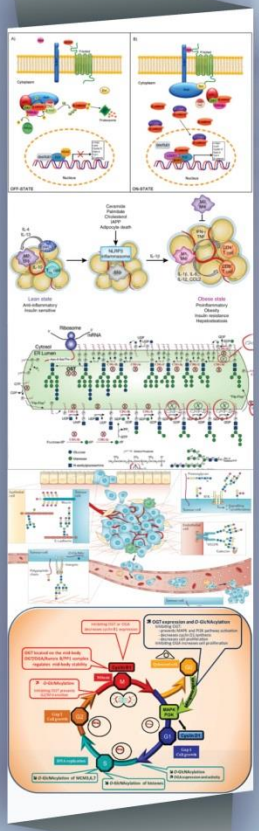
Cáncer, diabetes y obesidad: una oportunidad para la Glicociencia

27|OCTUBRE|2016

8-14 h | EDIFICIO DE POSGRADO UNAM



9:00 | Inauguración

9:15 | **Dysregulation of O-GlcNAcylation cycling in the etiology of obesity, type-2 diabetes and cancer**
Dr. Tony LEFEBVRE
Université de Lille - Sciences et Technologies

10:15 | **Intracellular heparan sulfates and related sulfotransferases: critical elements in the tauopathy neurodegenerative process**
Dra. Dulce Papy-García
Université Paris-Est Créteil Val de Marne (UPEC)

11:00 | Coffee break

11:15 | **O-GlcNAcylation: a new link between nutrition, epigenetics and cancer?**
Dra. Vanessa DEHENNAUT-LEFEBVRE
Institut de Biologie de Lille

12:00 | **Expression of galectin 9 in cervicouterine cancer**
Dra. Verónica Vallejo-Ruíz
Centro de Investigación Biomédica de Oriente I, IMSS

13:00 | **Heparan sulfate, a potential mediator of pro-survival signals during early Human Papillomavirus infection**
Dra. Leticia Rocha Zavaleta.
Instituto de Investigaciones Biomédicas, UNAM

14:00 | Clausura

Informes:
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Dysregulation of O-GlcNAcylation cycling in the etiology of obesity, type-2 diabetes and cancer

Steffi Baldini, Agata Steenackers, Maïté Leturcq, Ninon Véry, Moyira Aquino-Gil, Anne-Sophie Vercoutter Edouart, Ikram El Yazidi, Annick Pierce and *Tony Lefebvre.*

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The post-translational modification (PTM) of proteins by O-linked β-N-acetylglucosamine (O-GlcNAc) is regulated by a unique couple of enzymes. O-GlcNAc transferase (OGT) transfers the GlcNAc residue from UDP-GlcNAc, the final product of the hexosamine biosynthetic pathway (HBP), whereas O-GlcNAcase (OGA) removes it. O-GlcNAcylation occurs virtually in all living beings tested while a doubt remains for plants and yeasts. Also this modification intervenes in almost all biological processes and a deregulation of its dynamics actively participates in metabolic disorders and tumorigenesis. A synergy between unhealthy diet, obesity, diabetes and cancer emergence has been longstanding proposed, and part of the common molecular mechanism governing these pathologies may reside in the status of UDP-GlcNAc, the substrate of OGT, that is positioned at the crossroad of metabolic pathways. Recently our team focused on the regulation of FAS (fatty acid synthase) by O-GlcNAcylation. FAS is pivotal for de novo lipogenesis. Loss of control of this metabolic pathway contributes to development of liver pathologies ranging from steatosis to nonalcoholic steatohepatitis (NASH) which can lead to cirrhosis and less frequently to hepatocellular carcinoma. We demonstrate that expression and activity of liver FAS correlates with O-GlcNAcylation contents in ob/ob mice and in mice fed a high-carbohydrate diet both in a transcription-dependent and -independent manner. More importantly, inhibiting the removal of O-GlcNAc residues in mice intraperitoneally injected with the selective and potent OGA inhibitor Thiamet-G increases FAS expression. FAS and OGT physically interact and FAS is O-GlcNAc-modified. Treatment of a liver cell line with drugs or nutrients that elevate the O-GlcNAcylation interfere with FAS expression. Inhibition of OGA increases the interaction between FAS and the deubiquitinase Ubiquitin-specific protease-2a (USP2A) in vivo and ex vivo, providing mechanistic insights into the control of FAS expression through O-GlcNAcylation. These results reveal a new type of regulation of FAS, linked to O-GlcNAcylation status and advance our knowledge on deregulation of lipogenesis in diverse forms of liver diseases. We also hypothesized that the activity of FAS is regulated by O-GlcNAcylation during cell cycle progress. Cancers cells are characterized by their high capability to proliferate and by their high consumption of Glucose and Glutamine (part of the Warburg effect), two substrates of HBP. This imposes on accelerating membrane compounds biosynthesis to respond to the need of increasing membrane surface of dividing cells and to remodeling the structure of lipids microdomains. Attention has been paid to the up-regulation of O-GlcNAcylation processes observed in cancer cells lines that harbor higher levels of OGT and O-GlcNAcylation to fulfill their proliferative and migratory properties. Like OGT, expression and catalytic activity of both FAS are high in cancer cells but the reciprocal regulation of the two enzymes remains unexplored.

Intracellular heparan sulfates and related sulfotransferases: critical elements in the process leading to tauopathy

Dulce Papy-Garcia

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University Paris Est Créteil

Heparan sulfates (HS), the glycan chains in heparan sulfate proteoglycans (HSPG), are a family of complex polysaccharides which structural diversity allows specific interactions with several proteins involved in the regulation of tissue homeostasis, as growth factor and cytokines, and with proteins involved in neurodegenerative processes, as tau. The implication of HS in the mechanisms leading to tauopathies has been suggested by the HS co-localization and accumulation with tau and neurofibrillary tangles in neural cells of brains from Alzheimer's disease, which risk factors include ageing, heredity, and some pathologic conditions as high cholesterol, traumatic brain injury, and diabetes.

To investigate the role of HS in tau pathology, we first confirmed that internalization of membrane-associated HS, observed in Alzheimer's brain, effectively occurs in cell models of tauopathy. Our results suggested that upon interaction with HS at the intracellular level, tau follows conformational changes allowing the access of kinases to tau epitopes otherwise inaccessible for phosphorylation and, concomitantly, aggregation. In order to identify structural factors responsible of the HS–tau interaction, we studied expression of the biosynthetic HS sulfotransferases responsible of the generation of the HS structures involved in their interaction with tau in Alzheimer's disease. We found that the neural heparan sulfate sulfotransferase 2 (HS3ST2) showed to be increased in hippocampus from Alzheimer's disease. In vivo inhibition HS3ST2 in zebrafish and mice models of tauopathy resulted in strong reduction of abnormally phosphorylated tau epitopes with animal recovery. Our results suggest that 3-O-sulfated HS and the HS biosynthetic enzyme HS3ST2 are involved in the neurodegenerative process leading to AD.

O-GlcNAcylation: a new link between nutrition, epigenetics and colorectal cancer?

Amélie DECOURCELLE, Dominique LEPRINCE and *Vanessa DEHENNAUT*

CNRS-UMR 8161, Mechanisms of Tumorigenesis and Targetd Therapies, « Institut de Biologie de Lille », Lille Nord de France University, Pasteur Institute of Lille, IFR 142, 1 rue Calmette, BP447, 59017, Lille Cedex, France.

O-GlcNAcylation is a widespread post-translational modification that consists in the reversible linkage of a unique residue of N-acetylglucosamine (GlcNAc) onto serine and threonine residues of nucleocytoplasmic and mitochondrial proteins. The dynamic addition and removal of O-GlcNAc is governed by a unique couple of enzymes, O-GlcNAc transferase (OGT) and □-N-acetylglucosaminidase (OGA). The nucleotide-sugar UDP-GlcNAc, whose fluctuating levels reflect the nutrient flux within the cell, is the limiting substrate for O-GlcNAcylation processes. Therefore, UDP-GlcNAc and O-GlcNAcylation are considered as sensors of the nutritional status of the organism which can relieve the effects of an excessive food supply, malnutrition, obesity and other metabolic problems that represent high risk factors of colorectal cancers (CCR).

More and more studies sustain the existence of a close relationship between nutritional disorders, epigenetics modifications and etiology of CCR. However, the underlying mechanisms remain poorly understood.

It is now well established that OGT and O-GlcNAcylation are new cancer hallmarks. For instance, our previous works demonstrated that OGT and O-GlcNAcylation levels were increased in human colon tumors and colons from mice fed high-carbohydrate diets in comparison with healthy tissues and mice fed a standard diet, respectively. We also showed that knocking-down OGT in colon cancer cells decreased their proliferation, migration and invasiveness.

In recent years, O-GlcNAcylation has also emerged has an important regulator of chromatin dynamics and gene expression notably by being part of the “histone code” and through its interaction with the Polycomb Repressive Complex 2 (PRC2).

Our recent findings showed that in colon cancer cells OGT and EZH2 (the methyl transferase of PRC2, that catalyzes the trimethylation of lysine 27 of histone H3 (H3K27Me3)) contribute jointly to the repression of the expression of UNC5A and SCUBE2 two tumor suppressor genes involved in the regulation of proliferation, migration and survival of these cells. Taken together, our results support that nutritional and metabolic disorders lead to aberrant OGT and EZH2 activity responsible for the repression of tumor suppressor genes contributing to the cancerization of the colonic mucosa.

Expression of Galectin-9 in cervical cancer

Verónica Vallejo.Ruiz

Centro de Investigaciones Biomédicas de Oriente (CIBIOR)

Instituto Mexicano del Seguro Social

Galectins are a group of proteins known for their ability to bind to β-galactoside sugars, while having selective preferences for complex glycan structures. Galectins can be found intracellularly, both in the cytoplasm and the nucleus and extracellularly. Galectins have a wide variety of functions including regulating adhesion, migration, polarity, chemotaxis, proliferation, apoptosis and differentiation. Galectins have been associated with cancer. Galectin-9 have been implicated in tumor growth, metastasis, and the level of expression has been related to tumor aggressiveness and response to therapy.

Galectin-9 is a tandem repeat galectin, consisting of two carbohydrate-binding domains covalently bound by a flexible linker peptide. This protein is coded by the LGALS9 gene, this gene can express multiple RNA variants which codified protein products that exert diverging functions, because of the size of the linker peptide or the truncation of the carbohydrate-domain C-terminal.

In cervical cancer tissue, has been reported a decreased expression of Galectin-9. These results are related with the decreased levels of mRNA that we detected in cervical tissue. We characterized in cervical cell lines the presence of the transcript variants of LGALS9 and the protein isoforms. We detected 8 transcripts, but only 3 protein isoforms. As part of this study we determined the galectin-9 concentration in serum of women with normal cytology, low grade squamous intraepithelial lesions, high grade squamous intraepithelial lesions and cervical cancer. The concentration of galectin-9 was increased in women with cervical cancer with respect to control group. It is important to mention that some women with high grade squamous intraepithelial lesions had increased levels of this protein. The results obtained suggest that the galectin-9 could be a biomarker for cervical cancer.

Heparan sulfate, a potential mediator of pro-survival signals during early Human Papillomavirus infection

Leticia Rocha Zavaleta

Institute of Biomedical Research. National University of Mexico.

Infection by oncogenic types of Human Papillomavirus (HPV), such as HPV18, is strongly associated with the development of cervical cancer. HPV-mediated carcinogenesis has been widely investigated. However, less is known about the molecular effects produced by HPV during early infection. It has been proposed that HPV infects target epithelial cells by binding of viral capsid proteins to α6 -integrin and/or heparan sulfate. Here, we studied the effect of early HPV18 infection on the expression of the anti-apoptotic protein survivin, and the potential participation of heparan sulfate on the activation of this pro-survival protein. HPV18 pseudo-capsids, lacking the viral genome, were used to infect the human keratinocytes cell line HaCat. Expression of survivin was significantly increased after infection. Moreover, we detected that survivin was phosphorylated at the Thr34 residue. Thr34-phosphorylation induces the activation of survivin capacity to inhibit apoptosis. Pre-incubation of cells with heparinase abolished HPV18-induced increment of survivin expression and activation. In order to evaluate the effect of survivin activation, the cells were infected with HPV18 pseudo-capsids and then exposed to cisplatin. The cytotoxic effect of cisplatin was significantly reduced in infected cells. Our results suggest that binding of HPV18 capsids to heparin sulfate induces the expression of pro-survival signals during early infection of human cells, the study of the mechanism regulating this effect is currently in progress.