XXV Lección Conmemorativa Severo Ochoa

Viernes, 26 de octubre de 2108, Sala Ramón Areces, 12:00 h,

Centro de Biología Molecular Severo Ochoa

Título: Elucidation of cellular oxygen sensing pathways in human and animal cells: implications for physiology and medicine

Sir Peter Ratcliffe

Francis Crick Institute and Oxford University

Sir Peter Ratcliffe estudió medicina en Gonville y Caius College (Cambridge) y en el hospital de San Bartolomé (Londres). Posteriormente se especializó en Nefrología en la Universidad de Oxford donde comenzó a estudiar los mecanismos moleculares de la síntesis del factor hematopoyético eritropoyetina (EPO) en el riñón en respuesta a hipoxia. Este trabajo condujo al descubrimiento clave de que la respuesta a hipoxia es un fenómeno general que afecta a todos los tejidos y muchos tipos celulares y que se encuentra finamente regulado. El Dr. Ratcliffe y su grupo definieron a la familia de las prolil-hidroxilasas como sensores clave en la respuesta a hipoxia al regular la hidroxilación de la familia HIF de factores de transcripción, también esenciales en la respuesta a las modificaciones de los niveles de oxígeno tisular. La señalización celular en respuesta a hipoxia es fundamental en procesos biológicos críticos como el balance energético y la angiogénesis tumoral.

Sir Peter ha recibido numerosas distinciones y premios incluyendo la pertenencia a la Royal Society, el nombramiento de “caballero” en 2014 y el premio Lasker en 2016. Ha sido el director del departamento de Medicina Clínica Nuffield en Oxford entre 2004 y 2016 y en 2016 fue nombrado Director de Investigación Clínica en el Instituto Francis Crick de Londres, manteniendo una posición en Oxford como miembro del Instituto Ludwig y Director del Instituto de “Target Discovery”.

Estos descubrimientos han impactado de lleno en campos afines incluyendo el metabolismo y la biología redox, estableciendo nexos importantes entre la glucolisis, la bioenergética mitocondrial y la regulación por HIF. Además, la fisiopatología de problemas clínicos como la anemia, la disfunción vascular y la angiogénesis tumoral se han beneficiado de modo directo de la comprensión de los mecanismos de respuesta a hipoxia.

English version:

Sir Peter Ratcliffe is a physician scientist who trained in medicine at Gonville and Caius College, Cambridge and St. Bartholomew's Hospital, London, before moving to Oxford to specialise in renal medicine. He became interested in the regulation of the haematopoietic growth factor erythropoietin, which is produced by the kidneys in response to reduced blood oxygen availability. This work led to the unexpected discovery that the oxygen sensing process underlying the regulation of erythropoietin operates across essentially all animal cells and that it directs a broad range of other cellular and systemic responses to

hypoxia, including altered energy metabolism and angiogenesis. The laboratory went on to elucidate the mechanism of 'oxygen sensing', an unprecedented mode of signal transduction mediated by oxygen-dependent catalysis of prolyl and asparaginyl hydroxylation at specific sites within the key transcription factor, HIF (hypoxia inducible factor).

Sir Peter was elected to the Fellowship of the Royal Society and to the Academy of Medical Sciences in 2002. He is a member of EMBO and a foreign honorary member of the American Academy of Arts and Sciences. His work on oxygen sensing has won a number of awards including the Louis-Jeantet Prize in Medicine, the Canada Gairdner International Award, and the Lasker Award for Basic Biomedical Research. He was knighted for services to medicine in the New Year's Honours, 2014.

In 2004, he was appointed Nuffield Professor of Clinical Medicine at the University of Oxford and served as Head of the Nuffield Department of Clinical Medicine from 2004-2016. In May 2016 he was appointed Director of Clinical Research at the Francis Crick Institute, retaining a position at Oxford as member of the Ludwig Institute of Cancer Research and Director of Oxford's Target Discovery Institute.

These discoveries have pervaded vicinal fields including those of metabolism and redox biology as they paved the way to establish important links between glycolysis, mitochondrial bioenergetics and HIF regulation. Moreover, clinical settings such as anemia, vascular dysfunction or tumor angiogenesis, have directly benefited from the comprehension of the hypoxia-related sensing mechanisms.

Publicaciones clave/ Key Publications:

Maxwell, P.H., Pugh, C.W., and Ratcliffe, P.J. (1993). Inducible operation of the erythropoietin 3' enhancer in multiple cell lines: evidence for a widespread oxygen-sensing mechanism. Proc. Natl. Acad. Sci. USA. 90, 2423-2427.

Maxwell, P.H., Wiesener, M.S., Chang, G.-W., Clifford, S.C., Vaux, E.C., Cockman, M.E., Wykoff, C.C., Pugh, C.W., Maher, E.R., and Ratcliffe, P.J. (1999). The tumour suppressor protein VHL targets hypoxia-inducible factors for oxygen-dependent proteolysis. Nature. 399, 271-275.

Jaakkola, P., Mole, D.R., Tian, Y.-M., Wilson, M.I., Gielbert, J., Gaskell, S.J., von Kriegsheim, A., Hebestreit, H.F., Mukherji, M., Schofield, C.J., Maxwell, P.H., Pugh, C.W., and Ratcliffe, P.J. (2001). Targeting of HIF-α to the von Hippel-Lindau ubiquitylation complex by O2-regulated prolyl hydroxylation. Science. 292, 468-472.

Epstein, A.C.R., Gleadle, J.M., McNeill, L.A., Hewitson, K.S., O'Rourke, J.F., Mole, D.R., Mukherji, M., Metzen, E., Wilson, M.I., Dhanda, A., Tian, Y.-M., Masson, N., Hamilton, D.L., Jaakkola, P., Barstead, R., Hodgkin, J., Maxwell, P.H., Pugh, C.W., Schofield, C.J., and Ratcliffe, P.J. (2001). C. elegans EGL-9 and mammalian homologs define a family of dioxygenases that regulate HIF by prolyl hydroxylation. Cell. 107, 43-54.

Cockman, M.E., Lancaster, D.E., Stolze, I.P., Hewitson, K.S., McDonough, M.A., Coleman, M.L., Coles, C.H., Yu, X., Hay, R.T., Ley, S.C., Pugh, C.W., Oldham, N.J., Masson, N., Schofield, C.J., and Ratcliffe, P.J. (2006). Post-translational hydroxylation of ankyrin repeats in IkB proteins by the HIF asparaginyl hydroxylases, FIH. Proc. Natl. Acad. Sci. USA 103, 14767-14722.