

How to shoot the messenger

EMBL scientists shed light on cellular communication systems involved in neurodegeneration, cancer and cardiovascular disease

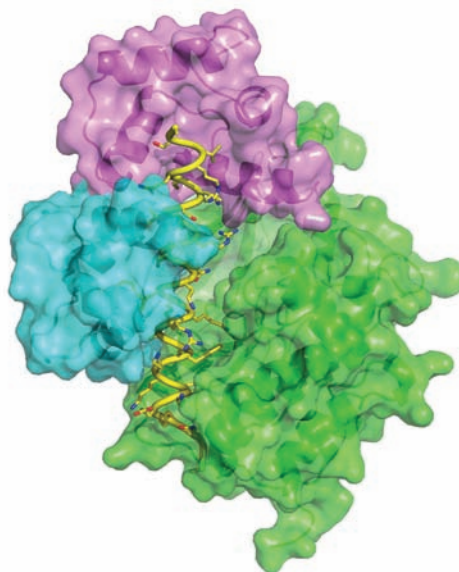
Hamburg, 26 January 2010 – Cells rely on a range of signalling systems to communicate with each other and to control their own internal workings. Scientists from the European Molecular Biology Laboratory (EMBL) in Hamburg, Germany, have now found a way to hack into a vital communications system, raising the possibility of developing new drugs to tackle disorders like neurodegeneration, cancer and cardiovascular disease. In a study published today in *Science Signaling*, they have pieced together the first snapshot of what two of the system's components look like while interacting.

One way these signalling systems work is by triggering a flood of calcium ions inside the cell. These get picked up by a receiver, a protein called calmodulin which turns this calcium signal into action by switching various parts of the cell's machinery on or off. Calmodulin regulates a set of proteins called kinases, each of which controls the activity of specific parts of the cell, thus altering the cell's behaviour.

Using high-energy X-rays produced by the European Synchrotron Radiation Facility (ESRF) in Grenoble, France, and by the German Synchrotron Radiation Centre (DESY), in Hamburg, Germany, Matthias Wilmanns' team at EMBL revealed the molecular structure of one of these kinases, a protein called Death-Associated Protein Kinase DAPK, when bound to calmodulin. The structure showed how calmodulin binds to a particular section of DAPK, switching the kinase on so that it can go and change the function of its targets. The team then worked out which of DAPK's building blocks, or amino acids, were crucial for calmodulin to bind.

"Faulty versions of DAPK are involved in the development of some cancers," says Wilmanns, "so we want to know more about how this protein functions to allow its better exploitation as an anti-cancer target."

What's more, DAPK has physical similarities to many of the



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This image shows the three-dimensional structure of Death-Associated Protein Kinase (green and yellow) when bound to calmodulin (violet and blue). It was obtained by X-ray crystallography.

other kinases controlled by calmodulin, meaning many of them are likely to interact with calmodulin in the same, or similar ways. Being able to see the three-dimensional structures of these proteins, how they clip together and alter each other's behaviour means researchers can devise ways to manipulate this interaction with drugs.

"That will provide a platform to get into drug discovery," says Wilmanns, adding, "obviously, this is the beginning of the story." He is planning to do so in an ongoing collaboration with Adi Kimchi's team at the Weizmann Institute in Israel and other groups from EMBL. ●

Source Article

De Diego, I., Kuper, J., Bakalova, N., Kursula, P., & Wilmanns, M. Molecular Basis of the Death Associated Protein Kinase – Calcium/Calmodulin regulator complex. *Science Signaling*, 26 January 2010.

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About EMBL

The European Molecular Biology Laboratory is a basic research institute funded by public research monies from 20 member states (Austria, Belgium, Croatia, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Luxembourg, the Netherlands, Norway, Portugal, Spain, Sweden, Switzerland and the United Kingdom) and associate member state Australia. Research at EMBL is conducted by approximately 80 independent groups covering the spectrum of molecular biology. The Laboratory has five units: the main Laboratory in Heidelberg, and Outstations in Hinxton (the European Bioinformatics Institute), Grenoble, Hamburg, and Monterotondo near Rome. The cornerstones of EMBL's mission are: to perform basic research in molecular biology; to train scientists, students and visitors at all levels; to offer vital services to scientists in the member states; to develop new instruments and methods in the life sciences and to actively engage in technology transfer activities. EMBL's International PhD Programme has a student body of about 170. The Laboratory also sponsors an active Science and Society programme. Visitors from the press and public are welcome.

About EMBL Hamburg

EMBL Hamburg is situated on the campus of the German Synchrotron Research Center (DESY) in Hamburg-Bahrenfeld, Germany. DESY hosts leading facilities for synchrotron radiation (DORIS-III, in operation, PETRA-III, under construction, user operation planned for 2009) and electron lasers (VUV-FEL, commissioned; X-FEL, planned). EMBL Hamburg operates seven experimental stations with applications in structural biology, using synchrotron radiation from the DORIS III ring. In addition, it runs a biochemistry laboratory hosting a pipeline for sample preparation and characterisation. It also includes facilities for high cell density fermentation, semi-automated protein purification and mass spectrometry. Start of operation of new state-of-the-art beamlines at the storage ring PETRA-3 is planned for 2009-2010. Research at EMBL Hamburg is tightly associated with the available synchrotron experiment stations for applications in life sciences. Several projects are aimed at developing novel technologies to advance methods in structural biology in terms of automation and user friendliness. In addition, faculty members from EMBL Hamburg lead a number of research projects to meet great challenges in structural biology. EMBL Hamburg provides a unique research environment for advanced training by hosting visits and offering specialised courses and workshops.

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