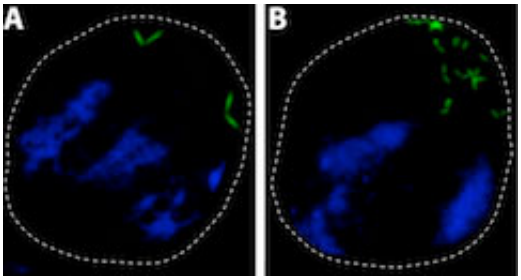
How protein suicide assure healthy cell structures

October 31 2013



Images of a sperm-precursor cell from the fruit fly, *Drosophila melanogaster*. A) Cells with normal levels of PLK4 protein have four centrioles (green); B) Cells with higher levels of PLK4 protein have extra-number of centrioles. Green and blue colors represent centrioles and DNA, respectively. Credit: Swadhin Jana, IGC.

Centrioles are tiny structures in the cell that play an important role in cell division and in the assembly of cilia and flagella. Changes in the number of centrioles are involved in diseases, such as cancer or infertility. Hence, the manipulation of these structures is being discussed for diagnosis and therapeutics. The regulation of centriole number has been further pinpointed in the latest issue of the scientific journal *Current Biology*. Researchers from Instituto Gulbenkian de Ciencia (IGC; Portugal), led by Monica Bettencourt-Dias, have now discovered that the master protein regulator in centriole formation, Polo-like kinase 4 (PLK4), needs to self-destruct in a regulated manner to ensure the presence of a normal number of centrioles in cells.

PLK4 is one of the key proteins required to control centriole formation: in its absence centrioles fail to form, while in excess PLK4 induces the formation of an extra number of those structures. Bettencourt-Dias' team has now identified how PLK4 controls its levels, and ultimately the number of centrioles. By performing different biochemical assays, the researchers observed that PLK4 is capable of auto-regulating its levels by adding chemical groups of phosphate to itself, which will act as a signal for destruction.

However, if PLK4 kills itself too early this will prevent it from ensuring the control of centriole number. Data obtained by the research team shows that the destruction mechanism undergoes a determined sequence of events that provides PLK4 with enough time for centriole number control before it is degraded. First, PLK4 acts by adding phosphate groups to other PLK4 proteins. In order for this to happen, different PLK4 proteins need to encounter themselves within the cell, which only occurs when a minimal amount of PLK4 is present. During the accumulation time, PLK4 is able to act in the formation of centrioles. Furthermore, the researchers discovered that phosphate groups were added to different sites of PLK4 under a specific order. Therefore the protein commits 'suicide', but in a controlled and timely fashion.

The research team then tested if this destruction mechanism had any implications in living organisms. Using as model organism the fruit fly, *Drosophila melanogaster*, they observed the natural existence of the destruction mechanism in different tissues of the fly. When this mechanism was abolished in female and male germ cells, precursors of eggs and sperm, it had an impact on the flies' fertility.

Ines Bento and Ines Cunha Ferreira, two of the authors of this work, say: "Our data indicates that PLK4 is a 'suicide' protein. Its activity determines its degradation. This is an important piece of a complex puzzle. But further research is required namely on how PLK4 regulation

is coordinated within the cycle of cell division."

Mónica Bettencourt-Dias adds: "The better we understand how PLK4 protein is regulated the more we perceive how the number of centrioles is controlled. It was recently announced that inhibition of PLK4 is going to clinical trials for breast cancer by researchers in Canada, so it is important to understand how this molecule is regulated."

More information: Cunha-Ferreira, I., Bento, I., Marques, A. P., Jana, S. C., Lince-Faria, M., Duarte, P., Borrego-Pinto, J., Gilberto, S., Amado, T., Brito, D., Rodrigues-Martins, A., Debski, J., Dzhindzhev, N., Bettencourt-Dias, M. Regulation of Autophosphorylation Controls PLK4 Self-Destruction and Centriole Number, *Current Biology* (2013), dx.doi.org/10.1016/j.cub.2013.09.037

Provided by Instituto Gulbenkian de Ciencia