Title:	Understanding mechanistic basis of regulation of cell growth by mitochondrial activity in Drosophila melanogaster
Authors:	Toshniwal, Ashish (/jspui/browse?type=author&value=Toshniwal%2C+Ashish)
Keywords:	Cell Growth Macromolecules Metabolites RNA Mitochondrial Function
Issue Date:	21-Nov-2019
Publisher:	IISERM
Abstract:	Cell growth, the process of attaining characteristic size and volume of a cell during development, is regulated by diverse cell intrinsic and cell extrinsic factors. The size of a cell is determined by the relative rates of synthesis, storage and turnover of macromolecules and metabolites. Studies in diverse cell lines and model organisms, ranging from yeast to rodents, have established that conserved Insulin/TOR cascade regulates cell growth by integrating nutrient availability and metabolism of the cell. Despite this, how functional status of mitochondria, the ware-house of metabolism, regulates cell growth is not well addressed. In this study, using genetically amenable model organism, Drosophila, a loss of function RNAi screen was performed to isolate nuclear genes encoding mitochondrial proteins that affect the overgrowth of adult eye, associated with over expression of Cyclin D and CDK4. As outcome of the screen, mitochondrial acyl carrier protein 1 (mtACP1), was identified as positive regulator of cell growth. mtACP1 is a well conserved protein that regulates mitochondrial fatty acid biosynthesis (FASII) and activity of Complex I of Electron Transport Chain. We show that loss of mtAcp1 increases ROS which reduces cell size by upregulation of 4EBP and downregulation of S6K and causes G1-S cell cycle arrest by upregulation of Dacapo, the p21 homolog in flies. Interestingly, the elevated levels of ROS activate JNK pathway which modulates cell growth without impinging into the conserved TOR cascade. The same signaling cascade, Ask1-JNK-FOXO senses the qualitative and quantitative differences in ROS to evoke differential cellular responses. Another exciting outcome of this work is, in response to ecdysone signaling, ROS causes the growth arrest in fat body cells, during development. We show that in this process, ROS activated JNK pathway is instrumental in attaining the balance of insulin/ecdysone signaling. Thus, this study defines an elegant mechanism where the threshold of ROS molecules generated, restricts cell growth during development and couples systemic growth to the development of the organism. Since the signaling cascades in growth regulation are conserved from Drosophila to humans and given the importance of mitochondrial function in healthy and pathophysiological conditions, our study holds far-reaching implications.

URI:	IISERM (IISERM) http://hdl.handle.net/123456789/1348 (http://hdl.handle.net/123456789/1348)
Appears in Collections:	PhD-2010 (/jspui/handle/123456789/952)

Files in This Item:

File	Description	Size	Format	
PH10057.pdf (/jspui/bitstream/123456789/1348/3/PH10057.pdf)		31.32 MB	Adobe PDF	View/Open (/jspui/bitstream/123456789/1348/3/

Show full item record (/jspui/handle/123456789/1348?mode=full)

(/jspui/handle/123456789/1348/statistics)

Admin Tools

Edit...

Export Item

Export (migrate) Item

Export metadata