Autophagy Provides Nutrients but Can Lead to Chop-Dependent Induction of Bim to Sensitize Growth Factor–Deprived Cells to Apoptosis

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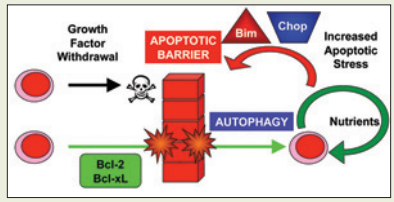
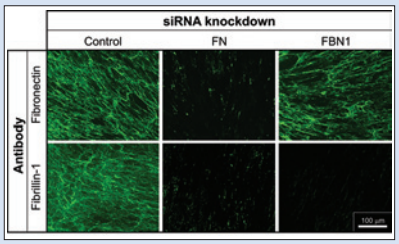


Tissue homeostasis is controlled by the availability of growth factors, which sustain exogenous nutrient uptake and prevent apoptosis. Thus apoptosis serves as a barrier to prevent survival of growth factor–deprived cells. Some cells express sufficient Bcl-2 or Bcl-xL to pass this apoptotic barrier and survive long-term growth factor deprivation. Autophagy has been proposed to provide nutrients for survival in such cases. Bcl-2 and Bcl-xL, however, have been shown to prevent autophagy in acute settings, making it unclear how cell metabolism is maintained in Bcl-2–mediated cell survival. The authors show that under conditions of growth factor withdrawal Bcl-2 and Bcl-xL do not prevent autophagy and that autophagy does indeed contribute to cell metabolism. Unexpectedly, autophagy also promotes induction of the pro-apoptotic protein Bim, thus sensitizing cells to apoptosis. This dual role for autophagy in cell survival may contribute to tissue homeostasis by sensitizing cells to apoptosis after growth factor withdrawal, ensuring that only the most apoptosis-resistant cells survive to utilize autophagy as a long-term survival mechanism.



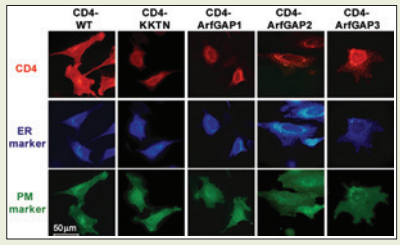
Fibrillin Assembly Requires Fibronectin

Laetitia Sabatier, Daliang Chen, Christine Fagotto-Kaufmann, Dirk Hubmacher, Marc D. McKee, Douglas S. Annis, Deane F. Mosher, and Dieter P. Reinhardt

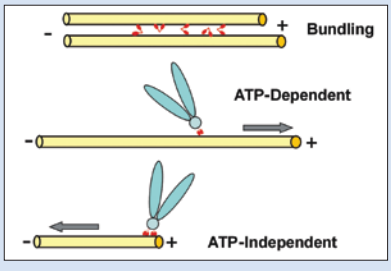
Multifunctional microfibrils are supramolecular machines in elastic and nonelastic extracellular matrices. Defective microfibrils give rise to various genetic connective tissue disorders, so-called fibrillinopathies, that affect the cardiovascular and skeletal system. Proper assembly mechanisms are central to the formation and function of these structures. Here, the authors use cell biological and biochemical approaches to identify critical components in the assembly of microfibrils and to demonstrate that a fibronectin network is an essential component in this process. By light and electron microscopy, they show that fibronectin co-localizes with fibrillin-1, one of the core components of microfibrils, in a cell culture model of microfibril assembly. Furthermore, they demonstrate that fibronectin interacts directly with all three members of the fibrillin family and that the interaction site localizes to the collagen/gelatin-binding region of fibronectin. Interestingly, fibrillins interact with fibronectin only when they are in a multimeric state involving 7–12 subunits, suggesting a highly regulated molecular assembly mechanism. These observations provide evidence that fibronectin is a master organizer in the assembly of microfibrils.

Discrete Determinants in ArfGAP2/3 Conferring Golgi Localization and Regulation by the COPI Coat

Lena Kliouchnikov, Joëlle Bigay, Bruno Mesmin, Anna Parnis, Moran Rawet, Noga Goldfeder, Bruno Antonny, and Dan Cassel



The budding of COPI-coated vesicles from the Golgi apparatus is coupled to the GTPase cycle of the small GTPase Arf1. Coat dissociation is regulated by three ArfGAPs, the previously characterized ArfGAP1 and the closely related ArfGAP2/3. To understand why there are multiple Golgi GAPs, the authors carried out comprehensive analysis of the ArfGAP3 protein. By means of an innovative strategy involving the retention of CD4-ArfGAP3 fusion constructs in the ER, they uncovered a central lysine-rich region in ArfGAP2/3 as important for binding to the COPI coatomer. Importantly, ArfGAP2/3 activity strictly depends on coat interaction that is mediated through this basic region. In contrast, the central region in ArfGAP1 contains amphipathic motifs that mediate the regulation of this protein by membrane curvature. The authors propose that regulation of vesicle uncoating is achieved by a combination of the two types of ArfGAPs, one sensing membrane deformation and the other the protein coat.



Kinesin-8 from Fission Yeast: A Heterodimeric, Plus End–Directed Motor that Can Couple Microtubule Depolymerization to Cargo Movement

Paula M. Grissom, Thomas A. Fiedler, Ekaterina L. Grishchuk, Daniela Nicastro, Robert R. West, and J. Richard McIntosh

Chromosome congression and segregation require the attachment of kinetochores to spindle microtubules (MTs). MT-associated proteins, including motor enzymes, are likely components of these attachments. Kinesin-8, part of the kinesin super-family, plays a role in organized chromosome motion in a variety of organisms. Previous work identified two kinesin-8s in fission yeast that colocalize with spindle MTs and kinetochores during mitosis. Here the authors demonstrate that these proteins, coexpressed in insect cells, form soluble heterodimers that show both microtubule-activated ATPase and ATP-dependent, plus end–directed motor activities. In the absence of ATP, this heterodimer can also support processive, minus end–directed motion of microbeads with the shortening ends of dynamic MTs. This kinesin may therefore be an important part of the machinery that assures the productive attachment of chromosomes to spindle fibers; it may aid both plus end–directed motions toward the spindle equator and minus end–directed motions toward the spindle poles. ■