

FEATURES

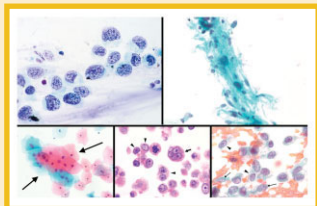
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The Cytologic Criteria of Malignancy

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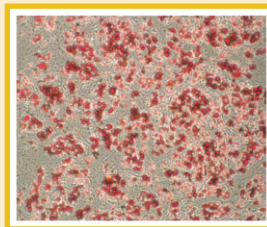
Cytology is the field of medicine in which various morphologic “criteria of malignancy” are applied to individual cells and small tissue fragments to diagnose cancer. Surprisingly little is known about the molecular basis of many of these defining structural features. In an effort to begin to develop common ground between cytology and cell biology, members of the American Society of Cytopathology Cell Biology Liaison Working Group classify the criteria of malignancy into three Groups and discuss how these criteria relate to current cell biology concepts. Criteria in Group 1 comprise tissue-level architectural alterations. Group 2 reflect genetic instability. Group 3 criteria are subcellular structural changes involving the cytoplasm, nuclear lamina, chromatin and nucleoli that cannot be attributed to genetic instability. Important criteria in Group 3 are directly induced by cancer genes, yet do not appear to relate to known cancer hallmark physiologies. The proposed classification provides a biologically relevant framework, independent of the histogenetic classification, for establishing common ground between cytologists and cell biologists. Understanding these criteria at a molecular level would provide an objective means for improving diagnosis and likely expose novel cellular mechanisms in cancer development.

miRNA Control of Adipocytes

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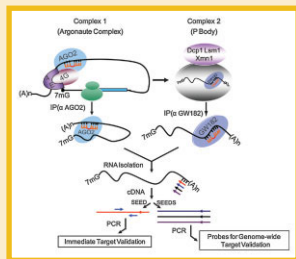
MicroRNA (miRNA) have been previously found to play important roles in a variety of physiologic processes. Recently, reports of alterations in miRNA expression levels in cultured pre-adipogenic cell lines during differentiation have suggested that miRNA molecules might regulate adipocyte differentiation and the formation of adipose tissue. However, direct evidence that miRNAs regulate adipogenesis is lacking. To determine if miRNA biogenesis governs adipocyte differentiation, Mudhasani and coworkers utilized primary cells isolated from mice bearing conditional alleles of Dicer, a cellular enzyme required for the processing of pre-miRNA molecules into mature miRNA. Their results demonstrate that Dicer is required for adipogenic differentiation of mouse embryonic fibroblasts and primary cultures of pre-adipocytes. Although deletion of Dicer in primary cells has been reported to induce premature cell senescence, the block to adipocyte differentiation imposed by Dicer ablation is not due to alteration of cell proliferation, as co-deletion of the *Ink4a* locus fails to rescue adipogenic differentiation in Dicer-null fibroblasts and pre-adipocytes. Collectively, these results reveal a requirement for Dicer and miRNA biogenesis in adipocyte differentiation.

Identifying miRNA Targets In Vivo

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A novel Ribonucleoprotein Immunoprecipitation (RNP-IP) method has been developed to isolate miR-RISC complexes, associated microRNAs and target mRNAs. This method characterizes mRNAs present in immunoprecipitates containing miR-RISC complexes that are obtained using GW182 and AGO2 antibodies. MicroRNA bound transcripts are reverse transcribed and amplified using seed sequence and 3'UTR derived primers. This flexible IP-based assay is a straightforward method to identify miRs participating in gene regulation and their cognate mRNAs in real time.

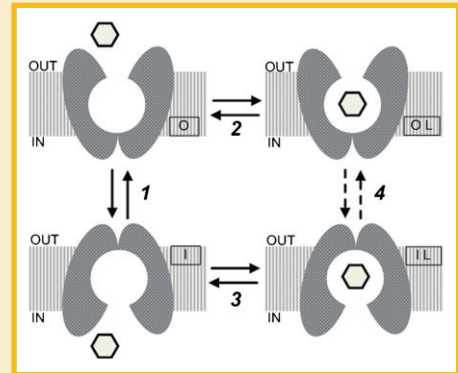
Intracellular Glucose Signaling

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920

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The importance of glucose homeostasis in human blood is well known and well studied. Intracellular glucose homeostasis is less studied because of technical challenges in measuring concentrations of nutrients and metabolites that have high turnover rates. The yeast *Saccharomyces cerevisiae* possesses a non-transporting, transporter-like glucose sensor, Snf3, known to mediate a response to extracellular glucose consisting in signaling for synthesis of glucose transporters, resulting in increased glucose uptake. Using intracellular cleavage of maltose into glucose in a mutant lacking glucose transporters, Karhumaa et al. have now found that intracellular glucose inhibits the Snf3-mediated signaling triggered by extracellular glucose, a phenomenon that is likely to contribute significantly to intracellular glucose homeostasis. This discovery of a new regulatory interaction in central carbon metabolism may help engineering of glycolytic flux for optimization of yields and/or productivities of fermentations. The authors propose that an inward-facing, non-signaling conformation of Snf3 binds intracellular glucose, which thereby disfavors an outward-facing or occluded signaling conformation of Snf3. Such a mechanism would conform to models for transporter-like sensors previously proposed on the basis of the behavior of non-transporting (Ssy1) and transporting (Gap1) amino acid sensors.



ILK and Bone Resorption

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960

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Osteoclastic bone resorption requires matrix recognition and attachment of the osteoclast through the $\alpha_v\beta_3$ integrin, which induces the assembly of multiprotein complexes that transduce downstream signals. A component of these complexes is the multifunctional protein Integrin-Linked Kinase (ILK), which interacts with the cytoplasmic β_3 integrin domain. The contribution of ILK-mediated signaling to resorptive activity is unknown and was addressed by Dossa et al. using tissue-specific inactivation of *Ilk*. Osteoclast-specific *Ilk* mutant mice had increased bone volume and an augmented number of osteoclasts that had decreased resorption activity. Compound heterozygous mice in which one allele of *Ilk* and one allele of the β_3 integrin gene were inactivated showed a partial phenocopy, confirming that β_3 integrin and *Ilk* form part of the same genetic cascade. Dossa et al. results thus show that ILK is important for the function, but not the differentiation, of osteoclasts and identify a novel target that could be pharmacologically manipulated to modulate bone resorption.

