

FEATURES

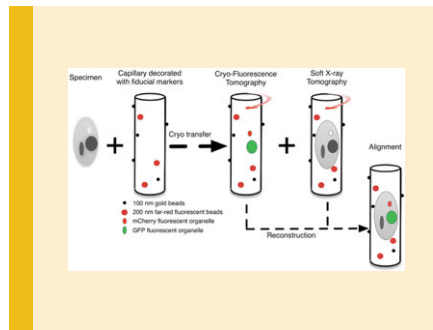
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Putting Molecules in Their Place

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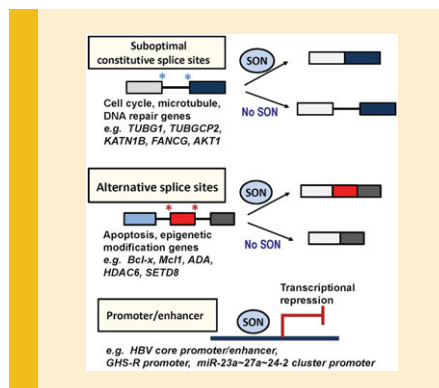
Each class of microscope is limited to imaging specific aspects of cell structure and/or molecular organization. However, imaging the specimen by complementary microscopies and correlating the data can overcome this limitation. Whilst not a new approach, the field of correlative imaging is currently benefitting from the emergence of new microscope techniques such as the correlation of cryogenic fluorescence tomography (CFT) with soft x-ray tomography (SXT). This amalgamation of techniques integrates 3-D molecular localization data (CFT) with a high-resolution, 3-D cell reconstruction of the cell (SXT). Cells are imaged in both modalities in a near-native, cryopreserved state. The authors describe the current state of the art in correlative CFT-SXT, and discuss the future outlook for this method.

New Discoveries of Old SON: A Link Between RNA Splicing and Cancer

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The SON protein is a ubiquitously expressed DNA- and RNA-binding protein primarily localized to nuclear speckles. Although several early studies implicated SON in DNA-binding, tumorigenesis and apoptosis, functional significance of this protein had not been recognized until recent studies discovered SON as a novel RNA splicing co-factor. During constitutive RNA splicing, SON ensures efficient intron removal from the transcripts containing suboptimal splice sites. Importantly, SON-mediated splicing is required for proper processing of selective transcripts related to cell cycle, microtubules/centrosomes maintenance, and genome stability. Moreover, SON regulates alternative splicing of RNAs from the genes involved in apoptosis and epigenetic modification. In addition to the role in RNA splicing, SON has an ability to suppress transcriptional activation at certain promoter/enhancer DNA sequences. Considering the multiple SON target genes which are directly involved in cell proliferation, genome stability and chromatin modifications, SON is an emerging player in gene regulation during cancer development and progression. The investigators summarize available information from several early studies on SON, and highlight recent discoveries describing molecular mechanisms of SON-mediated gene regulation. It is proposed that future efforts in better understanding the diverse functions of SON will reveal novel targets for cancer therapy.

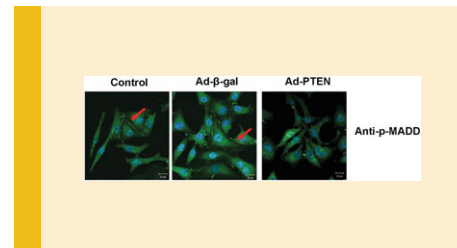
MADD Is a Downstream Target of PTEN in Triggering Apoptosis

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Mitogen-activated kinase activating death domain containing protein (MADD) is abundantly expressed in cancer cells and necessary for maintaining cancer cell survival. However, this survival function of MADD is dependent upon its phosphorylation by protein kinase B (Akt). The tumour suppressor PTEN (phosphatase and tensin homolog deleted on chromosome 10) is a lipid phosphatase that negatively regulates the phosphatidylinositol 3-kinase (PI3K)-Akt signalling pathway. The downstream targets of PTEN in triggering apoptosis have not yet been completely identified. The authors report that MADD can act as a pro-apoptotic factor to initiate apoptosis when its phosphorylation is attenuated by PTEN. The data shows that tumor necrosis factor α -related apoptosis-inducing ligand (TRAIL) induces a reduction in MADD phosphorylation with a concomitant up-regulation of PTEN. Knock down of PTEN using a specific siRNA prevents TRAIL-induced reduction in pMADD levels. Surprisingly, Akt non-phosphorylated MADD translocates from the plasma membrane to cytoplasm where it is bound to 14-3-3 and displaces 14-3-3 associated Bax, which translocates to mitochondria resulting in cytochrome-C release. Taken together, the data reveals that PTEN can convey the death signal by preventing MADD phosphorylation by Akt.



Human Wharton's Jelly Stem Cells and Its Conditioned Medium Enhance Healing Of Excisional and Diabetic Wounds

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Wound healing is a major problem in diabetic patients and current treatments have met with limited success. The following evaluates the treatment of excisional and diabetic wounds using a stem cell isolated from the human umbilical cord Wharton's jelly (hWJSC) that shares unique properties with embryonic and adult mesenchymal stem cells. hWJSCs are non-controversial, available in abundance, hypo-immunogenic, non-tumorigenic, differentiate into keratinocytes and secrete important molecules for tissue repair. When human skin fibroblasts (CCD) in conventional scratch-wound assays were exposed to hWJSC-conditioned medium (hWJSC-CM) the fibroblasts at the wound edges migrated and completely covered the spaces by day 2 compared to controls. The number of invaded cells, cell viability, total collagen, elastin and fibronectin levels were significantly greater in the hWJSC-CM treatment arm compared to controls ($p < 0.05$). When a single application of green fluorescent protein (GFP)-labelled hWJSCs (GFP-hWJSCs) or hWJSC-CM was administered to full-thickness murine excisional and diabetic wounds, healing rates were significantly greater compared to controls ($p < 0.05$). Wound biopsies collected at various time points showed the presence of green GFP-labelled hWJSCs, positive human keratinocyte markers (cytokeratin, involucrin, filaggrin) and expression of ICAM-1, TIMP-1 and VEGF-A. On histology, the GFP-hWJSCs and hWJSC-CM treated wounds showed reepithelialization, increased vascularity and cellular density and increased sebaceous gland and hair follicle numbers compared to controls. hWJSCs showed increased expression of several miRNAs associated with wound healing compared to CCDs. The studies demonstrate that hWJSCs enhance healing of excisional and diabetic wounds via differentiation into keratinocytes and release important molecules.

