

FEATURES

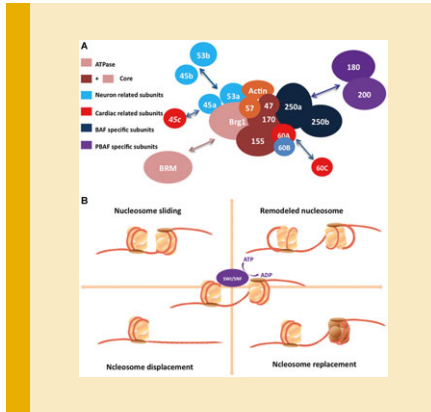
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SWI/SNF in Cardiac Progenitor Cell Differentiation

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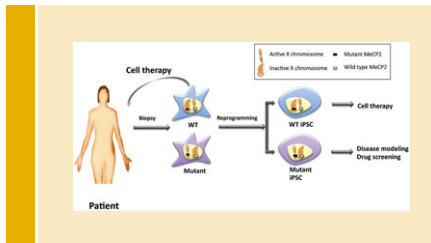
Cardiogenesis requires proper specification, proliferation, and differentiation of cardiac progenitor cells (CPCs). The differentiation of CPCs to specific cardiac cell types is likely guided by a comprehensive network comprised of cardiac transcription factors and epigenetic complexes. In this review, how the ATP-dependent chromatin remodeling SWI/SNF complexes work synergistically with transcription and epigenetic factors to direct specific cardiac gene expression during CPC differentiation is described. Furthermore, it is discussed how SWI/SNF may prime chromatin for cardiac gene expression at a genome-wide level. A detailed understanding of SWI/SNF-mediated CPC differentiation will provide important insight into the etiology of cardiac defects and help design novel therapies for heart disease.

Investigation of Rett Syndrome Using Pluripotent Stem Cells

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Rett syndrome (RTT) is one of most prevalent female neurodevelopmental disorders. De novo mutations in X-linked MECP2 are mostly responsible for RTT. Since the identification of MeCP2 as the underlying cause of RTT, murine models have contributed to understanding the pathophysiology of RTT and function of MeCP2. Reprogramming is a procedure to produce induced pluripotent stem cells (iPSCs) by overexpression of four transcription factors. iPSCs obtain similar features as embryonic stem cells and are capable of self-renewing and differentiating into cells of all three layers. iPSCs have been utilized in modeling human diseases in vitro. Neurons differentiated from RTT-iPSCs showed the recapitulation of RTT phenotypes. Despite the early success, genetic and epigenetic instability upon reprogramming and ensuing maintenance of iPSCs raise concerns in using RTT-iPSCs as an accurate in vitro model. Here, the current iPSC-based RTT modeling and its concerns and challenges is updated.

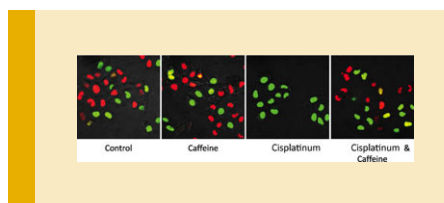
Dynamic Color-Coded Fluorescence Imaging of the Cell-Cycle Phase, Mitosis, and Apoptosis Demonstrates How Caffeine Modulates Cisplatin Efficacy

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Shinji Miwa, Shuya Yano, Yasunori Tome, Naotoshi Sugimoto, Yukihiko Hiroshima, Fuminari Uehara, Sumiyuki Mii, Hiroaki Kimura, Katsuhiro Hayashi, Elena V. Efimova, Toshiyoshi Fujiwara, Hiroyuki Tsuchiya, and Robert M. Hoffman

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Caffeine enhances the effect of certain anticancer drugs, but the mechanism of modulation is poorly understood. In this study, modulation of cisplatin efficacy induced by caffeine was visualized at the subcellular level by real-time fluorescent-protein imaging. Mitotic and apoptotic changes were observed by imaging 143B human osteosarcoma dual-color cells, in which GFP is expressed in the nucleus and RFP is expressed in the cytoplasm. Modulation of the cell cycle was imaged using time-lapse imaging of HeLa cells expressing a fluorescent ubiquitination-based cell cycle indicator (FUCCI) in the nucleus. Clonogenic assays showed that caffeine increased the inhibition by cisplatin on cell proliferation. Subcellular imaging demonstrated that cisplatin decreased mitosis and induced apoptosis in 143B cells. The combination of cisplatin and caffeine enhanced mitosis and subsequently increased apoptosis. Time-lapse imaging showed that cisplatin strongly induced cell-cycle arrest in the S/G2 phase in HeLa-FUCCI cells. Caffeine overcame the cell-cycle arrest induced by cisplatin, thereby increasing its efficacy, since cisplatin is ineffective against quiescent cells. The data in this report indicate that caffeine modulates the cell cycle in cancer cells, thereby enhancing efficacy of cell-cycle-dependent anticancer drugs such as cisplatin.



Imaging UVC-Induced DNA Damage Response in Models of Minimal Cancer

2493

Shinji Miwa, Shuya Yano, Yukihiko Hiroshima, Yasunori Tome, Fuminari Uehara, Sumiyuki Mii, Elena V. Efimova, Hiroaki Kimura, Katsuhiro Hayashi, Hiroyuki Tsuchiya, and Robert M. Hoffman

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It has been previously demonstrated that the ultraviolet (UV) light is effective against a variety of cancer cells in vivo as well as in vitro. In the present report, DNA damage repair response of minimal cancer after UVC irradiation is imaged. DNA-damage repair response to UV irradiation was imaged on tumors growing in 3D culture and in superficial tumors grown in vivo. UV-induced DNA damage repair was imaged with GFP fused to the DNA damage response (DDR)-related chromatin-binding protein 53BP1 in MiaPaCa-2 human pancreatic cancer cells. Three-dimensional Gelfoam® histocultures and confocal imaging enabled 53BP1-GFP nuclear foci to be observed within 1 h after UVC irradiation, indicating the onset of DNA damage repair response. A clonogenic assay showed that UVC inhibited MiaPaCa-2 cell proliferation in a dose-dependent manner, while UVA and UVB showed little effect on cell proliferation. Induction of UV-induced 53BP1-GFP focus formation was limited up to a depth of 40 mm in 3D-culture of MiaPaCa-2 cells. The MiaPaCa-2 cells irradiated by UVC light in a skin-flap mouse model had a significant decrease of tumor growth compared to untreated controls. Results also demonstrate that 53BP1-GFP is an imageable marker of UV-induced DNA damage repair response of minimal cancer and that UVC is a useful tool for the treatment of residual cancer since UVC can kill superficial cancer cells without damage to deep tissue.

