

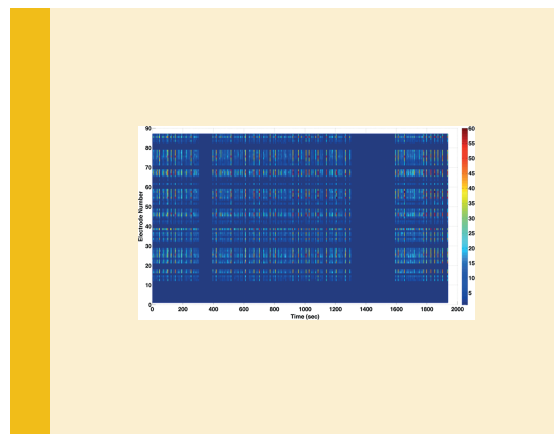
Comparative Analysis of Human and Rodent Brain Primary Neuronal Culture Spontaneous Activity Using Micro-Electrode Array Technology

Alessandro Napoli and Iyad Obeid

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Electrical activity in embryonic brain tissue has typically been studied using Micro Electrode Array (MEA) technology to make dozens of simultaneous recordings from dissociated neuronal cultures, brain stem cell progenitors, or brain slices from fetal rodents. Although these rodent neuronal primary culture electrical properties are mostly investigated, it has not been yet established to what extent the electrical characteristics of rodent brain neuronal cultures can be generalized to those of humans. A direct comparison of spontaneous spiking activity between rodent and human primary neurons grown under the same in vitro conditions using MEA technology has never been carried out before and will be described in the present study. Human and rodent dissociated fetal brain neuronal cultures were established in-vitro by culturing on a glass grid of 60 planar microelectrodes neurons under identical conditions. Three different cultures of human neurons were produced from tissue sourced from a single aborted fetus (at 16–18 gestational weeks) and these were compared with seven different cultures of embryonic rat neurons (at 18 gestational days) originally isolated from a single rat. The results show that the human and rodent cultures behaved significantly differently.



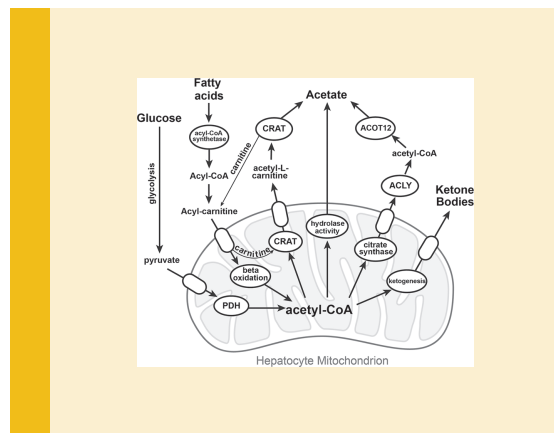
Acetate as a Metabolic and Epigenetic Modifier of Cancer Therapy

Diane M. Jaworski, Aryan M.A. Namboodiri, and John R. Moffett

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Metabolic networks are significantly altered in neoplastic cells. This altered metabolic program leads to increased glycolysis and lipogenesis and decreased dependence on oxidative phosphorylation and oxygen consumption. Despite their limited mitochondrial respiration, cancer cells, nonetheless, derive sufficient energy from alternative carbon sources and metabolic pathways to maintain cell proliferation. They do so, in part, by utilizing fatty acids, amino acids, ketone bodies, and acetate, in addition to glucose. The alternative pathways used in the metabolism of these carbon sources provide opportunities for therapeutic manipulation. Acetate, in particular, has garnered increased attention in the context of cancer as both an epigenetic regulator of posttranslational protein modification, and as a carbon source for cancer cell biomass accumulation. However, to date, the data have not provided a clear understanding of the precise roles that protein acetylation and acetate oxidation play in carcinogenesis, cancer progression or treatment. This review highlights some of the major issues, discrepancies, and opportunities associated with the manipulation of acetate metabolism and acetylation-based signaling in cancer development and treatment.



Converting Skin Fibroblasts into Hepatic-like Cells by Transient Programming

589

Xiang-Qing Zhu, Xing-Hua Pan, Ling Yao, Wei Li, Jiuwei Cui, Guanjun Wang, Randall J. Mrsny, Andrew R. Hoffman, and Ji-Fan Hu

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Transplantation of hepatocytes is a promising therapy for end-stage liver disease, but the availability of functional cells currently precludes its clinical application. We now report a simple transient reprogramming approach to convert fibroblasts into hepatic-like cells. Human skin fibroblasts were treated with fish egg extracts to become the transiently remodeled cells (TRCs). After infected with retroviral EGFP, they were directly injected into the fetal monkey liver, where they underwent in situ differentiation in the hepatic niche. The hepatic-like cells were functional as shown by the synthesis of hepatic markers in vivo, including albumin, cytokeratin-18, and hepatic serum antigen. Similarly, when implanted in the mouse liver, the TRCs were differentiated into hepatic-like cells that synthesize albumin and CK18 and became completely integrated into the liver parenchyma. The potency of TRCs was mechanistically related to the activation of several signal pathways, which reactivate endogenous genes related to cell potency. This study demonstrates the feasibility of a simple and inexpensive epigenetic remodeling approach to convert human fibroblasts into therapeutic hepatic-like cells for the treatment of end-stage liver disease.

The Glutamine–Alanine Repeat Domain of TCERG1 Is Required for the Inhibition of the Growth Arrest Activity of C/EBP α

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Nicholas J. Miller, Kaitlyn Schick, Nikolai Timchenko, Emmett Harrison, and William J. Roesler

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TCERG1 was characterized previously as a repressor of the transcription factor C/EBP α through a mechanism that involved relocalization of TCERG1 from nuclear speckles to pericentromeric regions. The inhibitory activity as well as the relocalization activity has been demonstrated to lie in the amino terminal half of the protein, which contains several discrete motifs including an imperfect glutamine-alanine (QA) repeat. In the present study, we showed that deletion of this domain completely abrogated the ability of TCERG1 to inhibit the growth arrest activity of C/EBP α . Moreover, the QA repeat deletion mutant of TCERG1 lost the ability to be relocalized from nuclear speckles to pericentromeric regions, and caused an increase in the average size of individual speckles. We also showed that deletion of the QA repeat abrogated the complex formation between TCERG1 and C/EBP α . Examination of mutants with varying numbers of QA repeats indicated that a minimal number of repeats are required for inhibitory activity as well as relocalization ability. These data contribute to our overall understanding of how TCERG1 can have gene-specific effects in addition to its more general roles in coordinating transcription elongation and splicing.