Role of Reactive Oxygen Species in Injury-Induced Insulin Resistance

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Acute insulin resistance is common after injury, infection, and critical illness. To investigate the role of reactive oxygen species (ROS) in critical illness diabetes, we measured hepatic ROS, which rapidly increased in mouse liver. Overexpressing LRP in these cells increases MMP-2 production specifically, while a laminin-binding deficient LRP does not. Importantly, LRP siRNA treatment abolishes GnRH-II-induced MMP-2 production, and inhibition in OVCAR-3 and CaOV-3 cells, which was also seen after MMP-2 siRNA treatment. These results suggest that GnRH-II–induced LRP expression increases the amount of the 67-kDa nonintegrin laminin receptor, which appears to interact with laminin in the extracellular matrix to promote MMP-2 expression and enhance ovarian cancer cell invasion.

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N-Cadherin Loss in POMC-Expressing Cells Leads to Pituitary Disorganization

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Pituitary tumors are the third most common intracranial tumor in humans and can cause altered hormone secretions leading to hypercortisolism, acromegaly, and infertility. Reduced expression of the cell adhesion molecule N-cadherin has been linked with the formation of pituitary tumors, but its role in normal pituitary gland physiology or tumor initiation is unknown. In the murine pituitary, N-cadherin expression is detected in virtually all cells of the posterior, intermediate, and anterior lobes. N-cadherin may function to initiate important cues such as controlling proliferation, directing cell placement, and promoting formation of cell networks that coordinate release of hormones into the bloodstream. To address this, we generated mice lacking N-cadherin in proopiomelanocortin-expressing melanotrope and corticotrope cells of the intermediate and anterior lobes of the pituitary. We observed that intermediate lobe cells can aberrantly displace Sry-type high-mobility-group box transcription factor 2-containing progenitor cells in the N-cadherin cadherin knockout mice at postnatal d 1. By postnatal d 30, although a reduction in α- and β-catenin membrane staining occurs, there is little effect on intermediate lobe architecture with N-cadherin loss. Also, despite these changes in adherens junction molecules, no alterations in cell proliferation occur. In contrast, loss of N-cadherin in the corticotropes leads to aberrant cell clustering and a reduction in Pomc mRNA. Taken together, our data reveal important roles of N-cadherin in pituitary cell placement and that loss of N-cadherin alone does not lead to pituitary tumor formation.

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Dynamic Chromatin Modifications Control GnRH Gene Expression during Neuronal Differentiation and Protein Kinase C Signal Transduction

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GnRH, a neuropeptide produced by rare, specialized hypothalamic secretory neurons, is critical for reproduction. During development, GnRH gene expression increases as neurons migrate from the olfactory placode to the hypothalamus, with highest levels in the mature, postmitotic state. While neuronal differentiation is known to be controlled by chromatin modulations, the role of chromatin dynamics in GnRH gene regulation has not been studied. Here, we use mature and immature GnRH neuronal cell models to show that both neuron-specific and protein kinase C regulation of GnRH expression are mediated by chromatin structure and histone modifications. Only in GT1-7 mature GnRH neuronal cells did GnRH regulatory elements display high sensitivity to DNase and enrichment of active histone markers histone-H3 acetylation and H3 lysine 4 trimethylation (H3K4-Me3), as well as RNA Polymerase II (RNAPII) binding and enhancer RNA transcription. In contrast, H3K9-Me2, a marker of inactive chromatin, was highest in nonneuronal cells, low in GT1-7 cells, and intermediate in immature GnRH neuronal cells. The chromatin of the GnRH gene was therefore active in mature GnRH neuronal cells, inactive in nonneuronal cells, but not fully inactive in immature GnRH neuronal cells. Activation of protein kinase C (PKC) potently represses GnRH expression. PKC activation caused closing of the chromatin and decreased RNAPII occupancy at the GnRH minimal promoter (−278/−97). At GnRH-Enhancer-1 (−2404/−2100), PKC activation decreased phosphorylated-RNAPII binding, enhancer RNA transcription, and H3 acetylation, and reciprocally increased H3K9-Me2. Chromatin modifications therefore participate in the dynamic regulation and specification of GnRH expression to differentiated hypothalamic neurons.

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Relationship between Vitamin D, Parathyroid Hormone, and Bone Health

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Context: There is a controversy regarding the definition of vitamin D insufficiency as it relates to bone health.