glucocorticoid, or with vehicle as a control, NTC cells had 2039 Dex-regulated genes, while Dex was still able to regulate 1087 genes in GRKD cells. Of these 1087 genes, 895 genes were uniquely regulated by Dex in GRKD cells suggesting that glucocorticoids might be signaling through another receptor in corneal epithelial cells. The top canonical pathways predicted to be altered by Dex in GRKD cells included PI3K/ATK Signaling, ERK5 Signaling, Prostrate Cancer Signaling, Aldosterone Signaling in Epithelial Cells, and PPAR signaling. These findings suggest that Dex could regulate large cohorts of genes through other nuclear receptors in corneal epithelial cells. Given the wide use of ophthalmic Dex in forms including eyedrops, ointments, gels, and implants, it is of clinical significance to understand the molecular actions of synthetic glucocorticoids since they appear to be ligands for multiple nuclear receptors in ocular cells and tissues.

Steroid Hormones and Receptors

STEROID HORMONES, NUCLEAR RECEPTORS, AND COLLABORATORS

Glucocorticoid Receptor Condensates Link DNA-Dependent Receptor Dimerization and Transcriptional Transactivation

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The glucocorticoid receptor (GR) is a ligand-regulated transcription factor (TF) that controls the tissue- and gene-specific transactivation and transrepression of thousands of target genes. Distinct GR DNA binding sequences with activating or repressive activities have been identified, but how they modulate transcription in opposite ways is not known. We show that GR forms phase-separated condensates that specifically concentrate known co-regulators via their intrinsically disordered regions (IDRs) in vitro. A combination of dynamic, multivalent (between IDRs) and specific, stable interactions (between LxxLL motifs and the GR ligand binding domain) control the degree of recruitment. Importantly, GR DNA-binding directs the selective partitioning of co-regulators within GR condensates such that activating DNAs cause enhanced recruitment of co-activators. Our work shows that condensation controls GR function by modulating co-regulator recruitment and provides a mechanism for the up- and down-regulation of GR target genes controlled by distinct DNA recognition elements.

Steroid Hormones and Receptors

STEROID HORMONES, NUCLEAR RECEPTORS, AND COLLABORATORS

Improving the Diagnosis, Treatment, and Prevention of Endocrine Diseases Through Accurate and Reliable Laboratory Measurements With CDC Clinical Standardization Programs

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Laboratory measurements are critical for correct diagnosis and treatment of patients with chronic diseases such as hypogonadism, PCOS, and thyroid diseases. Inaccurate measurements of disease biomarkers can lead to misclassification of patients/incorrect treatment and prevent the effective use of research findings in patient care. The CDC Clinical Standardization Programs (CDC CSP) improve the accuracy and reliability of clinical biomarker measurements by assessing and improving the analytical performance of assays. The CDC CSP assist with assay calibration, the certification of analytical performance, and the monitoring of routine patient and research testing. The CDC CSP work with clinical/research laboratories and assay manufacturers to improve laboratory measurements. Its current programs include the following analytes: total testosterone (TT), estradiol (E2), vitamin D (VD), free thyroxine (FT4), total cholesterol (TC), total glycerides (TG), HDL-cholesterol (HDL-C), and LDL-cholesterol (LDL-C). The work is being conducted through certification/monitoring programs and technical assistance. Most assays participating in the certification programs have seen performance improvements and maintain performance over time by continuous participation. Most major commercial laboratories and assays manufactures are enrolled in the certification programs. Currently certified and non-certified assays are available. Assays certified by CDC CSP are listed on the website at https://www.cdc.gov/labstandards/hs.html. The CDC Lipid Standardization Programs and CDC Accuracy-based Monitoring Programs allow for weekly monitoring of analytical performance of routine tests for analytes including TT, VD, TC, TG, HDL-C, apolipoprotein A1 and B. These monitoring programs assist researchers with assessing measurement accuracy of research studies over time and across laboratories. The CDC CSP also support accuracy-based external quality assurance surveys such as those offered by the College of American Pathologists (CAP). The CDC CSP assist researchers and stakeholders with developing and establishing reference intervals and conducting studies to better assess and diagnose patients. Based on the needs and requests from clinical community, programs for new biomarkers such as Lp(a), PTH and glucose are being developed. The CDC CSP work with stakeholders, such as the Endocrine Society and the Partnership for the Accurate Testing of Hormones, to educate the clinical and laboratory communities about the importance of using standardized assays in patient care, research, and public health.

Steroid Hormones and Receptors

STEROID HORMONES, NUCLEAR RECEPTORS, AND COLLABORATORS

Inhibition of Estrogen Signaling Reverses Established Inguinal Hernias

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Background: An inguinal hernia occurs when an intestinal loop or fat pushes through a weak spot in the lower abdominal muscle (LAM), causing a painful bulge that has the potential to cause bowel obstruction. Despite a high prevalence in men (~25%), non-surgical approaches are not available to treat this disease. We recently found a critical role of estrogen and estrogen receptor alpha (ERα) in inguinal hernia formation. To examine this further, we use a humanized aromatase mouse model (*Arom*^{hum}) where all of the male mice develop scrotal hernias as a pre-clinical model to test the first pharmacological intervention for inguinal hernias. These mice are utilized because their skeletal muscle tissue contains aromatase and produces estradiol (E2), which acts via ERα in the LAM stromal fibroblasts and leads to fibrosis and muscle atrophy. **Hypothesis:** E2-ERα modulation can inhibit and reverse the formation of inguinal hernias in *Arom*^{hum} mice by reducing LAM fibrosis and atrophy. **Results:** We tested three types of treatments to inhibit E2-ERα signaling: letrozole, fulvestrant, and raloxifene. Letrozole, an aromatase inhibitor, was shown to inhibit hernia formation and reversed small (150-175 mm^2) scrotal hernias (n = 10-15/group, p<0.0001). The LAM tissues also showed a reduction in fibrosis (n = 5-8/group, p = 0.0004) and a concurrent increase in myofiber cross-sectional area (n = 5-8, p=0.0356) compared to placebo-treated mice. Similarly, fulvestrant and raloxifene, E2-ERα antagonists, also inhibited hernia formation (n = 10-15/group). Most interestingly, both drugs reversed large and severe hernias (>200 mm^2, n = 10-15/group), accompanied by a decrease in muscle fibrosis and increase in myofiber cross-sectional area (ongoing study, n = 10-11, p<0.0001) compared to placebo mice. The drug-treated mice had lower expression of pro-fibrotic genes such as *Mmp3*, *Emb*, *Spon2*, *Timp1*, and *Tgfb1* in the LAM tissues compared to placebo-treated LAM. Furthermore, we analyzed the differences in extracellular matrix producing genes and muscle regeneration markers between the placebo and drug-treated muscle tissues. **Conclusion:** We find that inhibition of the E2-ERα signaling pathway can reverse mild or severe inguinal hernias. Successful treatment is accompanied by decreased skeletal muscle fibrosis and reversal of myocyte atrophy. These interventions are promising non-surgical treatment options for patients suffering from severe and recurrent inguinal hernias.

Steroid Hormones and Receptors

STEROID HORMONES, NUCLEAR RECEPTORS, AND COLLABORATORS

Investigating the Role Intestinal-Specific FXR and SHP in Regulating Lipid Metabolism in Mice

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Dysregulation of lipid metabolism is a causal factor that can lead to a variety of disorders, such as obesity and metabolic syndrome. Dietary fats are digested in the small intestine by the physiological detergents known as bile acids. They emulsify the fats and break them down into smaller molecules in order for the enterocytes to absorb the nutrients through simple diffusion or through the utilization of specific lipid transporters. Interestingly, the nuclear receptors farnesoid X receptor (FXR) and small heterodimer partner (SHP) not only regulates bile acid synthesis and circulation, but also lipid metabolism. Although many studies have examined the role of FXR in hepatic and intestinal lipid metabolism, studies investigating the role of SHP in the intestine are still lacking. Although FXR and SHP cooperate to regulate many metabolic pathways, FXR or SHP knockout models exhibit different lipid phenotypes. These data indicate there are FXR-dependent and -independent pathways of SHP that controls lipid metabolism. To delineate these two interconnecting yet separate pathways, we will utilize intestine-specific *Shp* knockout (*IShpKO*) and intestine-specific *Fxr* knockout (*IFxrKO*) mice model and place them on high fat diet to investigate their intestinal intestinal absorption and transportation of lipids. We will also monitor the bile acid pool in the intestine, serum, and liver in these knockouts to evaluate the consequence of intestinal deletion of *Fxr* as well as *Shp* on bile acid homeostasis and how this may affect lipid absorption. These experiments will identify how FXR and/or SHP regulates intestinal fat digestion and absorption and if this is secondary to the alterations in bile acid concentration and lipid transporters. In addition, we will also investigate the intestinal *Fxr-Shp* double knockout (*IDKO*) mice model to determine their combined contribution in intestinal lipid metabolism. Overall, the results obtained from this research will elucidate if intestinal FXR and SHP cooperate or can independently regulate lipid metabolism and homeostasis.

Steroid Hormones and Receptors

STEROID HORMONES, NUCLEAR RECEPTORS, AND COLLABORATORS

Investigating the Role of Farnesoid X Receptor in Heme Biosynthesis and Ductular Reaction

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Bile acids (BAs) have gained traction not just as emulsifiers of fat, but also as hormones. Nuclear receptor Farnesoid X receptor (FXR) is the master regulator of BAs and can also control glucose and lipid metabolism. We examined if FXR contributed towards heme biosynthesis and induction of a ductular reaction. Male and female whole body *Fxr* knockout (*Fxr*KO) mice, as well as liver- and intestine-specific knockouts (L*Fxr*KO and I*Fxr*KO, respectively) were treated with 3,5-diethoxycarbonyl-1,4-dihydrocollidine (DDC, a ferrochelatase inhibitor) for two weeks. At the end of the two weeks, mice were fasted for four hours and euthanized. All groups of mice had lost a similar percentage of body weight when fed the DDC diet. However, female *Fxr*KO mice had significantly increased liver to body weight ratio, while male *Fxr*KO mice had significantly decreased liver to body weight ratio when fed the DDC diet compared with their wild type counterparts. Serum liver injury markers were analyzed and liver histology and changes in genes involved in the heme biosynthesis pathway were examined. Both male and female whole body *Fx*rKO livers had decreased ductular reaction with minimal bile plugs