expression) and VCaP (high PAP expression). Castrated VCaP tumors underwent tumor stasis, were significantly smaller compared to intact mice, had decreased AR, PSA and ERG expression but persistent expression of PAP. Double staining of tumors for PAP and AR demonstrated a population of cells that were positive for PAP but negative for AR expression in hypoxic areas near necrosis. Inoculation of LNCaP cells with MC3T3 osteoblastic cells increased PAP expression *in vivo*.

Conclusions: PAP is expressed early in human fetal prostate development prior to the secretion of significant androgens or expression of AR. In mouse xenograft tumors and human PCa bone metastases, androgens did not significantly regulate PAP expression. Both hypoxia and stroma increased PAP expression. These data demonstrate that PAP is a marker of early progenitor cells, is persistently expressed after castration and is upregulated by tumor microenvironmental factors. PAP may be a suitable target for the treatment of castration-resistant metastatic disease.

Tumor Biology

HORMONE ACTIONS IN TUMOR BIOLOGY: FROM NEW MECHANISMS TO THERAPY

Protein Signatures of Parathyroid Carcinomas Using Proteomic Analyses

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Parathyroid carcinomas are rare endocrine tumors derived from the parathyroid glands with poor prognosis. Moreover, parathyroid carcinomas are resistant to radiation or drug therapy, and surgical resection is the only treatment option. Understanding the molecular pathogenesis of parathyroid carcinomas may pave the way for early diagnostic biomarkers and therapeutic targets. Therefore, we aimed to elucidate the protein signatures for parathyroid carcinomas through quantitative proteomic analyses. We performed liquid chromatography with tandem mass spectrometry (LC-MS/MS) technique with formalin-fixed paraffin-embedded (FFPE) samples and reached a quantitative depth of more than 5,000 proteins per sample. For the analyses, 23 parathyroid carcinoma and 15 adenoma samples were collected from five tertiary hospitals in Korea. Patients' mean age was 52 years, and 24 (63%) were female. Patients with parathyroid carcinoma had higher parathyroid hormone (PTH) and serum calcium level than adenomas (PTH, 1077.6 ± 760.7, 181.8 ± 139.8 pg/mL; calcium 13.0 ± 2.8, 11.3 ± 1.0 mg/dL, respectively). From the proteomic expression profiling, there were 137 differentially expressed proteins with the cutoff of both $p < 0.05$ and fold change > 1.5. Using the Ingenuity Pathway Analysis (IPA), top enriched canonical pathways in parathyroid carcinomas included glycoprotein-6 signaling related to the coagulation pathway, acute phase response, mTOR, and clathrin-/caveolar-mediated endocytosis signaling. In transcription factor analysis, TGFβ and TP53 were activated in carcinoma, and these factors were up-regulators of CD44 antigen and Annexin A2 (ANXA2) proteins. In network analysis, α-1-acid glycoprotein 1 (ORM1), laminin subunit β-2 (LAMB2), and Serpin family (SERPIN) proteins were derived as essential proteins and correlated to the AKT complex. Also, with the support vector machine (SVM)-based classification method, we derived a set of proteins that can discriminate carcinomas from adenomas, which consists of Carbonic anhydrase 4 (CA4), α/β hydrolase domain-containing protein 14B (ABHD14B), CD44, LAMB2, phosphatidylinositol transfer protein β isoform (PITPNB), and ORM1, with the lowest error rate of 11.1%. In conclusion, from the proteomics analyses of parathyroid neoplasms, newly recognized pathways - signaling related to coagulation, acute phase response, and endocytosis - were enriched in parathyroid carcinoma in addition to the known mTOR signaling pathway. The proteins such as α-1-acid glycoprotein and laminin subunit β-2 from SVM classification and network analyses could be the distinctive signature of carcinoma and may provide insights into the therapeutic target.

Tumor Biology

HORMONE ACTIONS IN TUMOR BIOLOGY: FROM NEW MECHANISMS TO THERAPY

Small Molecule Modulation of MEMO1 Protein-Protein Interactions

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MEMO1 (mediator of ErbB2-driven cell motility) is upregulated in breast tumors and has been correlated with poor prognosis in patients. As a scaffolding protein that binds to phosphorylated-tyrosine residues on receptors such as estrogen receptor and ErbB2, MEMO1 levels can influence phosphorylation cascades. Using our previously developed fluorescence polarization assay, we have identified small molecules with the ability to disrupt the interactions of MEMO1. We have performed limited structure-activity-relationship studies and computational analyses to investigate the molecular requirements for MEMO1 inhibition. The most promising compounds exhibit slowed migration of breast cancer cell lines (T47D and SKBR3) in a wound-healing assay emulating results obtained from the knockdown of MEMO1 protein. To our knowledge, these are the first small molecules targeting the MEMO1 protein-protein interface and therefore, will be invaluable tools for the investigation of the role of the MEMO1 in breast cancer and other biological contexts.

Tumor Biology

HORMONE ACTIONS IN TUMOR BIOLOGY: FROM NEW MECHANISMS TO THERAPY

Steroid Receptor Co-Activators Regulate Metabolic Kinases to Drive Therapy Resistant ER+ Breast Cancer

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Recurrence of metastatic breast cancer stemming from acquired endocrine and chemotherapy resistance remains a health burden for women with luminal (ER+) breast cancer. Disseminated ER+ tumor cells can remain viable but quiescent for years to decades. Contributing factors to metastatic spread include the maintenance and expansion of breast cancer stem cells (CSCs). Breast CSCs are poorly proliferative and frequently exist as a minority population in therapy resistant tumors. Our objective is to define novel signaling pathways that govern therapy resistance in ER+ breast cancer. In this study, we show that cytoplasmic complexes composed of steroid receptor (SR) co-activators, PELP1 and SRC-3, modulate breast CSC expansion through upregulation of the HIF-activated metabolic target genes *PFKFB3* and *PFKFB4*. Seahorse metabolic assays demonstrated that cytoplasmic PELP1 influences cellular metabolism by increasing both glycolysis and mitochondrial respiration. PELP1 interacts with PFKFB3 and PFKFB4 proteins, and inhibition of PFKFB3 and PFKFB4 kinase activity blocks PELP1-induced tumorspheres and protein-protein interactions with SRC-3. PFKFB4 knockdown inhibited *in vivo* emergence of circulating tumor cell (CTC) populations in ER+ mammary intraductal (MIND) xenografts. Application of PFKFB inhibitors in combination with ER targeted therapies blocked tumorsphere formation in multiple models of advanced breast cancer, including tamoxifen (TamR) and paclitaxel (TaxR) resistant models and ER+ patient-derived organoids (PDxO). Together, our data suggest that PELP1, SRC-3, and PFKFBs cooperate to drive ER+ tumor cells that include CSCs and CTCs. Identifying non-ER pharmacological targets offers a useful approach to blocking metastatic escape from standard of care ER/estrogen (E2)-targeted strategies to overcome endocrine and chemotherapy resistance in ER+ breast cancer.

Tumor Biology

HORMONE ACTIONS IN TUMOR BIOLOGY: FROM NEW MECHANISMS TO THERAPY

Stress-Induced Differential miR-4633-5p Expression in Thyroid Cancer Health Disparities

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Filipino Americans (FA) are known to have higher rates of thyroid cancer incidence and disease recurrence compared to European Americans (EA). FA are also known to be two times more likely to die of thyroid cancer compared to EA. Epidemiological studies in California have shown that thyroid cancer is the second most common cancer among FA women. Currently, there are no studies that demonstrate the mechanism behind these discrepancies. Evidence shows a strong correlation between obesity and more aggressive forms of thyroid cancer; obesity has an increased frequency in FA populations. The exact connection between the mechanisms of obesity and cancer is poorly understood. This epigenetic phenomenon may be due to microRNAs (miRNAs), which post-transcriptionally regulate gene expression. Dysregulated miRNA profiles have been associated with various diseases including obesity and cancer. MiRNAs are linked to different types of cancer; tumor suppressor genes and oncogenes are subject to modulation by dysregulated miRNAs. No study elucidates the association of miRNAs to tumor staging or prognosis in thyroid cancer health disparities. In this study, we determined miRNA expression profiles and found significant differences in the miRNA profiles between FA and EA thyroid cancer patients. Our pilot study showed several dysregulated miRNAs, from which we chose to assay dysregulated miR-4633-5p segments that are known to be associated with thyroid cancer signaling. We used QIAGEN's miRNA extraction kit to obtain high-quality miRNA from paraffin-embedded thyroid tissues. We performed next-generation miRNA sequencing using equal number of FA and EA samples and identified the top ten significantly up- and down-regulated miRNAs from the pool of differentially expressed miRNAs by qPCR assays. Our investigation demonstrated a 1.5-2-fold higher expression of an upregulated miR-4633-5p in FA versus EA miRNA samples (n=70) after normalized to controls. In contrast, miR-323b-3p showed no difference between FA and EA after normalized to controls. For our future work, we plan to analyze multiple up- and down-regulated miRNAs by qPCR, determine whether the miRNA signatures are consistent between samples from FA versus EA, and explore the use of these miRNA signature differentials for affordable and rapid thyroid cancer screening and prognosis.

Tumor Biology

HORMONE ACTIONS IN TUMOR BIOLOGY: FROM NEW MECHANISMS TO THERAPY

Systemic Immune Response in Murine Bilateral Pheochromocytoma Model During Immunotherapy Based on a Combination of Mannan-BAM, TLR Ligands and Anti-CD40 Antibodies (MBTA Therapy)

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