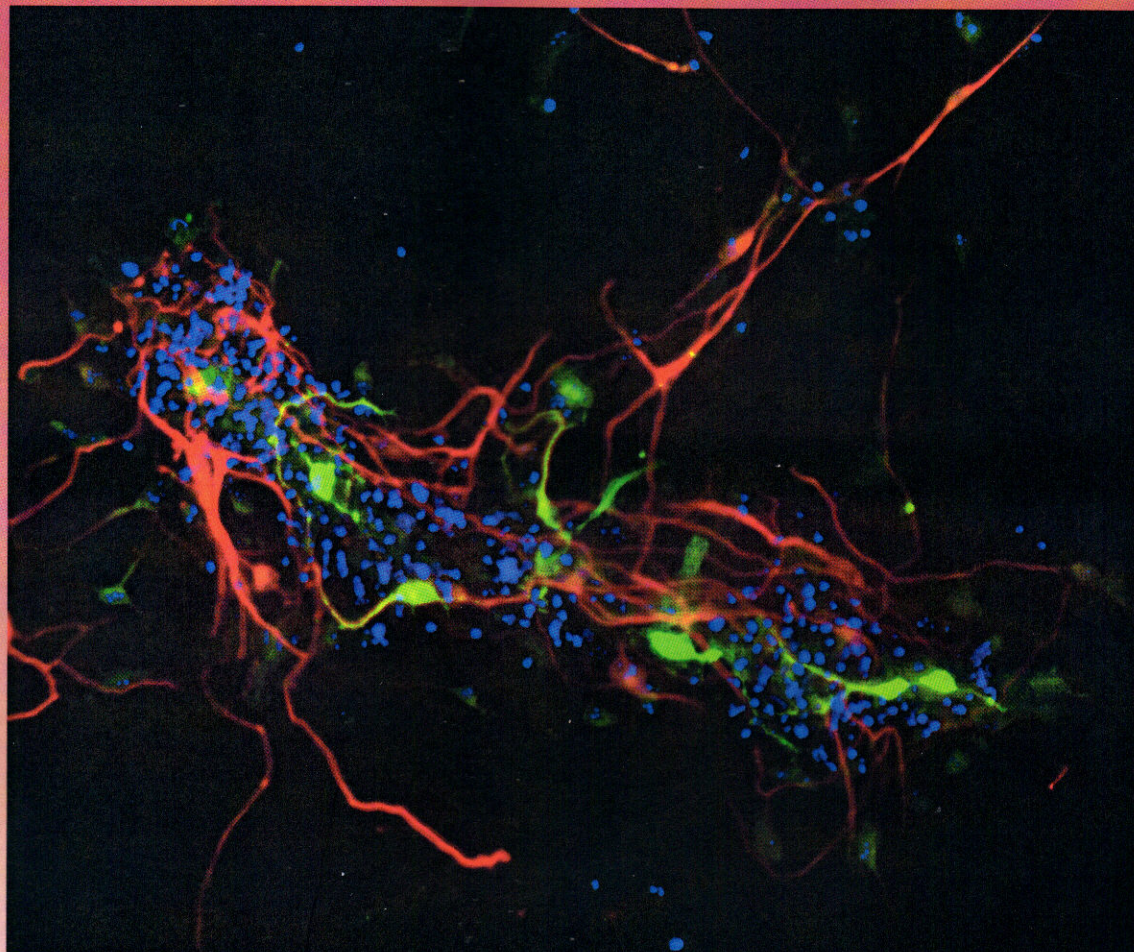


Abstracts of the 2nd Joint Meeting of Pathology And Laboratory Diagnostics



September 2014 | Volume 184 | Supplement

The American Journal of **PATHOLOGY**

Cellular and Molecular Biology of Disease

Official Journal of the American Society for Investigative Pathology

ajp.amjpathol.org

Results: This study presents an overview of available miRNA tools and databases that are specially designed to solve the puzzle related to how miRNAs affect human diseases.

Conclusions: Bioinformatic resources provide an important support to link between miRNA and human pathological disorders. It would further aid the clinical strategy for disease management.

AMT8. Lipid Storage and Annexin A3 in Clear Cell Renal Cell Carcinoma

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Background: Clear cell renal cell carcinoma (ccRCC) is characterized by cells with clear cytoplasm due to lipid and glycogen storage. VHL inactivation in 90% of sporadic ccRCC prevents degradation of HIF1 α /HIF2 α that activate hypoxia-inducible genes involved in metabolic alterations responsible also for "clear" cytoplasm. PPAR pathways, involved in adipocytic differentiation characterized by lipid droplet accumulation, are targeted to inhibit ccRCC cell growth and seem negatively regulated by annexin A3 protein (ANXA3), downregulated in ccRCC cells. By cytological, molecular, and functional approaches, we investigated annexin A3 involvement in lipid storage of ccRCC cells.

Methods: Primary cell cultures established from ccRCC and normal cortex tissues, and ccRCC cell lines were used. Lipid storage in cultures and corresponding tissues were evaluated by Oil Red "O" staining. AnxA3 expression was evaluated by western blot and immunofluorescence analysis and gene silencing was performed by siRNA. Cell viability was evaluated by MTT assay.

Results: ccRCC primary cultures maintain at the first passage the lipid storage observed in corresponding tissues. The downregulation of ANXA3 observed in ccRCC cells correlated with more abundant lipid storage. Annexin A3 gene silencing by siRNA induced in ccRCC cells an increase of lipid storage with a decrease of cell viability.

Conclusions: Our data show primary cell cultures as a reliable model to study the metabolic features of ccRCC and an involvement of annexin A3 in ccRCC modulation of lipid metabolism and storage. These data shed light on the molecular mechanisms involved in metabolic reprogramming of ccRCC and putative therapeutic targets. Supported by A.G.S. Onlus.

AMT9. Polymorphisms of Cytochrome P450 (CYP) Genes and Response to Chemotherapy in Patients with Colorectal Cancer (CRC)

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Background: Genes coding for the cytochrome P450 (CYP) enzyme system implied in antineoplastic drug metabolism pathways are highly polymorphic. This may influence both carcinogen metabolism and drug pharmacodynamics modifying their therapeutic efficacy and side effects.

Methods: We investigated the influence of genetic polymorphisms of CYP enzymes: rs1799853 (*CYP2C9*), rs35742686 (*CYP2D*), rs5030655 (*CYP2D6/3*), rs2740574 (*CYP3A4/1*) rs776746 (*CYP3A5*) on the response of chemotherapy and clinical outcomes, in a group of 56 patients affected by sporadic CRC, treated with the standard protocols. A total of 44 patients were in complete remission after treatment, 12 had persistence of the disease. Polymorphisms were typed using a competitive allele specific PCR assay (KASPar), developed by KBioscience. Statistical were analyzed using the χ^2 test with Yates correction and Fisher's Exact Test. Significance was defined as p values <0.05.

Results: No significant genetic contribute was observed for 4 of the 5 SNPs tested. A significant different genetic distribution between patients in complete remission after treatment and those of symptomatic patients was observed for the polymorphism C→T (rs1799853) responsible of an

Arg144Cys change in *CYP2C9* and associated with reduced enzyme activity (p=0.031, O.R.= 4.760, 95% C. I.: 1.237 to 18.311).

Conclusions: These results suggest that rs1799853 is a functionally relevant SNP of *CYP2C9* that may influence the efficacy of therapy. Thus, pharmacogenetic biomarkers have the potential of optimizing chemotherapy for individual patients.

AMT10. Biomarkers in Triple-Negative Breast Cancer

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Background: Breast cancer is the foremost cancer among women globally. Molecular profiling based on oestrogen and progesterone receptor expressions and *HER2* oncogene amplification is widely used to stratify breast cancer patients for targeted therapy. Triple-negative breast cancer (TNBC) does not express these markers. Comprising 10-20% of breast cancers, they pose a clinical challenge as they do not respond to hormonal and *HER2*-targeted agents.

Methods: A search for biomarkers predictive of response to chemotherapy is thus important.

Results: It is increasingly appreciated that TNBC is a heterogeneous disease, overlapping with *BRCA*-mutated and basal-like cancers. Studies are emerging that those with *BRCA1* mutation show better response to platinum-based chemotherapy, and that *BRCA* mutation may predict response to PARP inhibitors. Expression of basal markers, such as CK5, CK14, CK17, EGFR and e-cadherin, has been less hopeful in prediction of response to chemotherapy. Whereas Ki-67 proliferative rate and p53 mutation status have promise as prognostic markers, they have been less so as predictive markers. As upregulation of the phosphoinositide-3 kinase (PI3K) signaling pathway has been reported in TNBC, this has also been investigated for biomarker and drug development. Recent collaborative work at the University of Malaya revealed that phosphatase and tensin homolog (*PTEN*) loss is a frequent event in TNBC, and that this is associated with a younger age at cancer onset, late presentation stage, and high levels of insulin like growth factor-binding protein 2 (IGFBP2) expression.

Conclusions: Biomarker development in TNBC is relatively new, but has great potential because of great need.

AMT11. Resveratrol, Pyk2 and p66Shc: A Very Complicated "Dangerous Liaison"

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Background: Oxidative stress by triggering a host of pro-carcinogenic processes is a plausible link between nutrition and prostate cancer. Thus dietary antioxidants, such as resveratrol, are good candidates for chemoprevention. PYK2, a non-receptor tyrosine kinase activated among other stimuli by oxidative stress, once activated induces Shc tyrosine phosphorylation, which is a prerequisite for Ser 36 phosphorylation of p66Shc, a redox enzyme able to respond to oxidative stress and also to induce ROS production. Because the convergence of Pyk2 and Shc in the same pathway, their sensitivity to intracellular redox state and, the ability of resveratrol to influence redox state and to interfere with cell proliferation.

Methods: The relationship between resveratrol, Pyk2 and p66Shc in EPN cells, a human prostate cell line, and EPN-PKM3 cells bearing PKM, a dead kinase mutant of Pyk2 was examined. ROS production, cell proliferation, and resveratrol molecular targets were investigated.

Results: Here we show that resveratrol induces Pyk2 activation but blocks ERK activation in both in EPN and EPN-PKM3 cell lines and reversibly blocks EPN and EPN-PKM3 cell proliferation, although inducing Shc tyrosine phosphorylation. Furthermore, resveratrol-induced p66Shc