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Magayr, T., Streets, A. orcid.org/0000-0002-4328-044X and Ong, A. orcid.org/0000-0002-7211-5400 (2020) SAT-442 Identification of exosome microRNAs as novel biomarkers for rapid disease progression in autosomal dominant polycystic kidney disease. In: Kidney International Reports. ISN World Congress of Nephrology (ISN WCN '20), 26-29 Mar 2020, Abu Dhabi, United Arab Emirates. Elsevier , S185-S185.

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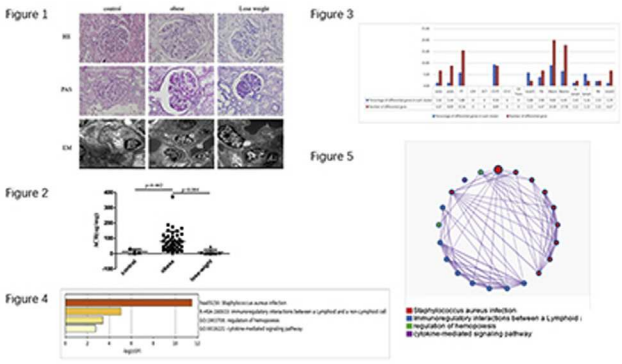

Conclusions: Activation of immune response in macrophages involved in the development of ORG. Losing weight is beneficial to retard even reverse the progression of ORG.

SAT-442

IDENTIFICATION OF EXOSOME MICRORNAS AS NOVEL BIOMARKERS FOR RAPID DISEASE PROGRESSION IN AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE

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Introduction: ADPKD is the most common renal genetic disease and the fourth most common cause of end-stage renal disease (ESRD) worldwide. Although *PKD1* and *PKD2* patients have different phenotypes, there is also significant intra-familial variability in disease progression suggesting that other genetic or environmental factors have major influences on disease progression. With the availability of new therapies, there is now an urgent need to identify novel biomarkers which can identify ADPKD patients at risk of rapid disease progression at an early stage of disease.

Methods: Spot urine specimens were collected from consecutive patients with ADPKD (n = 130) attending a PKD clinic at the Sheffield Kidney Institute and healthy controls (n = 33). Urinary exosomes were isolated by ultracentrifugation and confirmed by electron microscopy and western blotting. The detection and quantification of exosome-associated microRNAs in spot urine samples from healthy volunteers, ADPKD patients with early (eGFR > 60 ml/min) or late (eGFR < 60 ml/min) disease was by global RNA-sequencing. Of the differentially expressed microRNAs commonly identified by 3 algorithms, we chose several kidney-enriched microRNAs from the same family (miR-30) or located at the same gene cluster (miR-192/miR194) for further validation in a cohort of 60 participants using TaqMan qPCR assays.

Results: Electron microscopy confirmed the presence of multiple (<100 nm) vesicles in the pelleted fraction and western blotting detected the presence of the exosome specific protein TSG-101 in the pellet, demonstrating their origin from multivesicular bodies. In the discovery cohort (n=22), we identified a miRNA signature of down regulated exosome small RNAs compared to controls, including three members of the miR-30 family, miR-192-5p and miR-194-5p. All five kidney-enriched microRNAs were also decreased in a validation cohort (n=60). Significantly, their expression was negatively correlated with eGFR, positively correlated with mean kidney length, and were significantly better predictors of the rate of disease progression in ADPKD (eGFR slope < or >-3ml/min/year over 5 years) compared to mean kidney length by ROC analysis.

Conclusions: By global microRNA profiling, we have identified an exosome miRNA signature characteristic of ADPKD patients compared to healthy controls. Exosome expression of members of the miR-30 family, miR-192-5p and miR-194-5p out performed mean kidney length in identifying patients with rapid disease progression. Future studies will seek to validate these findings in additional patient cohorts and to compare their performance with that of other accepted or novel disease biomarkers. Our ultimate goal is to improve risk prediction in patients with early disease, to identify those who could benefit from earlier and more intensive intervention.

SAT-443

INTERDEPENDENT REGULATION OF POLYCYSTINS INFLUENCES AUTOPHAGY, CELL DEATH AND PROLIFERATION

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Introduction: Autosomal dominant polycystic kidney disease (ADPKD) is caused by mutations in either *PKD1* or *PKD2*, encoding for the proteins polycystin-1 (PC1) or polycystin-2 (PC2), respectively. The exact function of polycystins in cyst formation remains unclear. Renal stress has been proposed to enhance cystogenesis, while altered autophagy has recently been implicated in ADPKD progression. We therefore aimed to investigate the cellular response towards nutritional stress in mouse inner medullary collecting duct cells (IMCDs), either wild-type (WT) or lacking PC1 or PC2 (PC1KO or PC2KO), with a focus on cell survival (autophagy) and cell death (apoptosis). Results were validated in human urine-derived proximal tubular epithelial cells from early-stage ADPKD patients versus healthy individuals.

Methods: Autophagy was measured by LC3 immunoblotting and by counting GFP-LC3 punctae. Cell death was assessed by the levels of cleaved Caspase 3, FITC-Annexin V/PI staining and Trypan Blue exclusion assay.

Results: PC1KO and PC2KO IMCDs were more resistant against nutrient stress, with reduced cell death compared to WT following 72 h of starvation. Basal and starvation-induced autophagy (3 h) was enhanced in PC1KO, while the latter was suppressed in PC2KO IMCDs. However, 48 h following starvation, higher autophagy levels in both PC1KO and PC2KO IMCDs were observed compared to WT IMCDs, suggesting that polycystins regulate the transition from autophagy to cell death. Increased resistance towards starvation associated with elevated autophagy was also observed in human ADPKD cells. Inhibition of autophagy reduced nutrient stress resistance in the polycystin-deficient cells, suggesting that the increased survival is due to enhanced autophagy. Moreover, these findings were dependent on a reciprocal regulation of polycystins, in which PC1 suppresses PC2 and PC2 enhances PC1 levels during nutrient starvation. Interestingly, following recovery, PC1 KO showed higher proliferation and mTOR activity compared to WT IMCDs.

Conclusions: Our data suggest that PC1 and PC2 determine the cell death *versus* survival response during nutritional stress. As such, polycystin-deficient cells display suppressed apoptosis and enhanced autophagy resulting in more cell survival during nutrient starvation than WT cells. Consequently, polycystin-deficient cells have an increased proliferation rate following recovery from the stress. This mechanism suggests how stress is able to amplify cystogenesis in ADPKD.

SAT-444

GENOTYPE - PHENOTYPE CORRELATION IN A PEDIATRIC ADPKD COHORT

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