compared to baseline (+0.9%, 95% CI [-1.5, 3.3], P=0.46). FMD tended to increase after liraglutide and sitagliptin but was not significant (liraglutide +1.2 [-0.3, 2.8], P=0.12; sitagliptin +1.6 [-0.6, 3.8], P=0.15). Given that liraglutide and sitagliptin work through the same GLP-1 pathway, we combined the liraglutide and sitagliptin groups for overall effect on FMD, which was significantly improved from baseline (+1.4 [0.1, 2.8], P=0.04). Diet and liraglutide improved PAI-1
at 14 weeks (diet -4.4U/mL, [-8.5, -0.2], P=0.04; liraglutide -3.4 [-6.0, -0.7], P=0.01), while sitagliptin did not (-1.4 [-5.1, 2.3], P=0.46). DISCUSSION/SIGNIFICANCE: Activation of the GLP-1 pathway by liraglutide or sitagliptin improves FMD independent of weight loss, while PAI-1 improvement is weight-loss dependent and is only seen after liraglutide or diet. Our study suggests the cardiovascular benefit of liraglutide may be due to combined improvements in endothelial vasodilatory and fibrinolytic function.

420

Comparison of Statin Use to Non-Use on Cerebral Blood Flow Velocity in Older Adults at Risk for Alzheimers Disease: Data from a Phase II Multisite Clinical Trial

Stacey E. Aaron[1], Tsubasa Tomoto[2], Rong Zhang[2] and Sandra A. Billinger[1]
[1]University of Kansas Medical Center and [2]University of Texas Southwestern

OBJECTIVES/GOALS: Reduced cerebral blood flow (CBF) along with vascular risk factors (e.g., dyslipidemia) are prevalent in Alzheimers disease (AD) and related dementias. Statins are one of the most effective pharmacologic treatments for vascular risk reduction, which may contribute to CBF in individuals with an increased risk for AD. METHODS/STUDY POPULATION: Cross-sectional analysis of 212 older adults with a family history of dementia. Heart rate via electrocardiogram, mean arterial pressure (MAP) via brachial sphygmomanometers, end-tidal CO2 via capnograph, and CBF velocity at the middle cerebral artery (MCAv) via transcranial Doppler ultrasound were collected following 20-minutes of supine rest. Mean MCAv (cm/s) was measured within each cardiac cycle and averaged over an 8-minute duration. Cerebrovascular conductance was calculated by dividing mean MCAv by MAP. Pulsatility Index was calculated by subtracting systolic MCAv from diastolic MCAv and then dividing by mean MCAv. RESULTS/ANTICIPATED RESULTS: 125 females (68 Â± 6 years; 49 statin) and 87 males (70 Â± 6 years; 47 statin) were included in analyses. There were no significant differences between heart rate, MAP, or end-tidal CO2 between statin and non-statin users. After controlling for age, sex, and low-density and high-density lipoprotein, statin use did not significantly contribute to MCAv ($p = 0.09$). However, statin use did significantly contribute to cerebrovascular conductance (MCAv/MAP; $p = 0.03$) as well as Pulsatility Index (assessment of cerebral health, $p < 0.01$). DISCUSSION/SIGNIFICANCE: Our findings suggest statin use significantly and positively contributes to resting cerebral blood flow velocity and cerebrovascular health. Further investigation is warranted into statin interventions with other components of cerebrovascular function, as differences may have implications for brain health and disease pathogenesis.

421

Specific cephalosporin antibiotics deplete tumor PD-L1 to inhibit DNA damage sensing and sensitize to Chk1 inhibitors in vivo*

Clare Murray[1], Anand Kornepati[1], Alvaro Padron[1], Yilun Deng[1], Myrna Garcia[1], Haiyan Bai[1] and Tyler Curiel[1]
[1]UT Health San Antonio

OBJECTIVES/GOALS: Tumor PDL1 signals to immune cells for tumor immune evasion but has cell-intrinsic signals that promote tumor virulence. We identify novel tumor PDL1 depleting drugs (PDDs) to interrupt tumor-intrinsic PDL1 signals and sensitize tumors to targeted therapy in vitro and in vivo. METHODS/STUDY POPULATION: We screened the Prestwick and LOPAC libraries for FDA-approved drugs reducing B16 melanoma PDL1 > 2.6-fold. ?-lactam antibiotics were used at 80 ?M and Chk1 inhibitor rabusertib as indicated in T24 human bladder cancer, and murine ID8agg ovarian cancer, 4T1 breast cancer and B16. Genetic PDL1 KO was by CRISPR or shRNA and re-expression by lentivirus. Viability was by MTT and protein by immunoblot. We challenged 5 NSG mice/group with 2x106 T24 (SQ) cells and 5 BALB/c mice/group with 5x105 4T1 cells (mammary fat pad) and treated with cefepime (200 mg/kg), rabusertib (2.5 mg/kg), vehicle, or combo daily from day 3. RESULTS/ANTICIPATED RESULTS: Structurally-related ?-lactam antibiotics cefepime and ceftazidime are tumor PDDs. Cefepime or ceftazidime reduced tumor PD-L1 and thus its cell-intrinsic signals to deplete the DNA damage sensing Chk2 protein and promote rabusertib synthetic lethality in vitro and in vivo in a tumor PDL1-dependent manner independent of immunity. Structurally distinct ?-lactam antibiotics did not sensitize tumor cells to rabusertib, suggesting ?-lactam antimicrobial functions did not promote PDL1 depletion or rabusertib treatment effects in vivo. Although rabusertib effects were immune-independent, both PDDs induced immunogenic tumor STING signaling, suggesting they can improve tumor immunotherapy. DISCUSSION/SIGNIFICANCE: We show a rapidly translatable way to deplete detrimental tumor-intrinsic PDL1 signals, and sensitize tumors to rabusertib. We are testing PDD structure activity relationships to improve PDD effects and testing PDD effects on other treatments, e.g., PARP inhibitors, immunotherapy.

424

Considerations Mid-Translation of a Novel Extracellular Vesicle Product in Myocarditis

Danielle Beetler[1], Katelyn A. Bruno[1], Atta Behfar[1], Leslie T. Cooper[1] and DeLisa Fairweather[1]
[1]Mayo Clinic

OBJECTIVES/GOALS: Myocarditis is an inflammatory cardiomyopathy commonly caused by viral infections. The residual burden of this disease after guideline-based therapies is substantial, as there are no pathway-specific therapies. Our long-term goal is to find and translate treatments that reduce acute myocarditis severity and prevent progression of disease. METHODS/STUDY POPULATION: Of available therapies, extracellular vesicles (EVs) are ideally suited to the task of simultaneous, specific reprogramming of multiple

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