Endothelial microparticles reduce neointimal formation in a model of acute arterial injury in vivo and decrease proliferation and migration of vascular smooth muscle cells in vitro. The transfer of mir126 by EMP and subsequent regulation of LRPI6 expression in VSMCs might be a possible pathway.

**967 I BENCH**

Titrating connexin43 in immune cells decreases atherosclerotic plaque development in mice

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Purpose: Ubiquitous reduction of the gap junction protein connexin43 (Cx43) in mice provides beneficial effects on progression and composition of atherosclerotic lesions. Cx43 is expressed in multiple atheroma-associated cells, such as endothelial cells, smooth muscle cells and macrophages, but the exact contribution of Cx43 in each cell type during atherogenesis is not known.

Methods and results: To examine specifically the role of Cx43 in immune cells, low-density lipoprotein receptor-deficient mice were lethally irradiated and reconstituted with Cx43+/+, Cx43+/- or Cx43-/- hematopoietic fetal liver cells. Five weeks after reconstitution, mice received a cholesterol-rich diet (HCD) for 14 weeks. The three groups displayed similar increases in body weight and serum cholesterol after HCD. The progression of atherosclerosis (% lipid deposition) was significantly lower in aortic roots of Cx43+/- chimeras (11.4±1.0%; N=8; P<0.01) compared with Cx43+/+ (17.6±1.9%) and Cx43-/- (17.9±1.0%) chimeras. Plaque composition was comparable in the 3 groups for macrophages (CD68), T lymphocytes (CD4) and extracellular matrix (Masson Trichrome, Picosiris Red), but Cx43+/- chimeras' plaques contained significantly less neutrophils (Ly6G-positive, 3'UTR area; 1.9±0.7%; N=8; P<0.05) compared with Cx43+/+ (6.0±1.6%) and Cx43-/- (6.5±1.4%) chimeras' plaques. Surprisingly, neutrophils obtained from peripheral blood of control and hypercholesterolemic mice did not express Cx43. Functional tests for neutrophils (in vitro endothelial adhesion assay and in vivo vascular transmigration assay) showed no difference between neutrophils from Cx43+/+ and Cx43+/- mice. Finally, we observed less proliferating cells in bone marrow of Cx43+/+ and Cx43+/- chimeras in comparison to Cx43-/- chimeras, but the relative proportions of circulating neutrophils, lymphocytes and monocytes were similar between the 3 groups.

Conclusion: Our study shows that reduction of Cx43 expression in immune cells reduces atherosclerotic plaque formation and infiltration of neutrophils into the lesion, whereas deletion of Cx43 from immune cells abrogates this protective effect. As neutrophils are devoid of Cx43, our results warrant further studies towards a possible differential secretion of chemotactic molecules by other Cx43-expressing immune cells such as macrophages.

**968 I BENCH**

Poly(ADP-ribose) polymerase -14 interacts with tristetraprolin to selectively regulate tissue factor mRNA stability: a novel role for ADP-ribosylation in regulating mRNA turnover and thrombosis

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Background: Targeting post-transcriptional pathways is now emerging as a promising therapeutic strategy in a wide spectrum of diseases. Monocyte-derived tissue factor (TF) plays critical roles in atherothrombosis, but little is known about its post-transcriptional regulation. Tristetraprolin (TPP) is the most widely studied mRNA-binding protein, and binds to the 3'UTR of target mRNAs and promotes decay. Poly(ADP-ribose)-polymerase-14 (PARP-14, PARP-14) forms a 17 proteins with a PARP domain that generates poly(ADP-ribose) adducts on intracellular proteins – a post-translational modification implicated in diverse cellular functions.

Purpose: We sought to determine the roles for TPP and PARP-14 in regulating TF expression, and the role of ADP-ribosylation in modulating TF mRNA turnover.

Methods and results: TF mRNA and protein were increased in TTP-/- vs TTP+/- macrophages (p<0.05) with increased TF mRNA stability (t1/2=47±6.2min vs 82±14min; p<0.01). Similarly, TF mRNA and protein were increased in PARP-14/-/- vs PARP-14+/- macrophages (p<0.05) with increased TF mRNA stability (t1/2=181±11min vs 60±5min; p<0.001). TF mRNA, activity and protein were increased in vivo (heart, lung, kidney, aorta and unfractinated circulating leukocytes) in PARP-14/-/- vs PARP-14+/- mice (p<0.05). Intravital microscopy demonstrated a 66% reduction in median arteriolar occlusion time in LPS-stimulated PARP-14+/- vs PARP-14+/- mice (p=0.008). RNP immunoprecipitation and RNA binding pulldown assays demonstrated an interdependency for PARP-14 and TPP to form a ternary complex with TF mRNA, where both proteins interacted within the same 3'UTR segment. Inhibition of PARP activity reduced TF mRNA stability in PARP-14+/- macrophages (p<0.018), but not in PARP-14/-/- macrophages.

Rapid Fire – The new biology of atherosclerosis

**966 I BENCH**

MicroRNA-126-containing endothelial microparticles reduce neointimaformation and vascular smooth muscle cell proliferation

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Background: Vascular Smooth Muscle Cell (VSMC) proliferation is of importance in the pathogenesis of vascular diseases such as restenosis or atherosclerosis. Endothelial Microparticles (EMP) have been shown to promote vascular regeneration in vivo and not to be forgotten: Rapid Fire – The new biology of atherosclerosis

Conclusion: There were many mismatch diseases in severe coronary artery stenoses of non-LAD lesions. IVUS-MLA cannot accurately predict FFR. FFR measurement can prevent unnecessary PCI, especially in non-LAD lesions.

**RAPID FIRE – THE NEW BIOLOGY OF Atherosclerosis**

**965 I BEDSIDE**

The regional difference in severe coronary artery disease between fractional flow reserve and intravascular ultrasound

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Background: Both fractional flow reserve (FFR)-guided and intravascular ultrasound (IVUS)-guided strategies have been reported to safe and effective in coronary lesions. However, we are clinically in a dilemma between IVUS-lumen area (MLA) < 4.0mm² and FFR ≤ 0.80 (defined as “Mismatch diseases”) study. FFR was calculated after intracoronary administration of papaverine to induce maximal hyperemia. We divided into LAD and non-LAD lesions and compared a prevalence of mismatch diseases in LAD lesions and that in non-LAD lesions. The ROC analysis was performed to evaluate IVUS-MLA for estimating FFR≤0.80 in each lesions.

Result: A prevalence of mismatch diseases in non-LAD lesions was significantly higher in a model of LAD lesions (LAD vs. non-LAD; 21.2% vs. 67.8%, p<0.05). The best cutoff value of IVUS-MLA in FFR≤0.80 were also significantly different between LAD and non-LAD lesions (LAD vs non-LAD; 3.20mm² vs. 2.07mm², p<0.05).