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Pro-atherogenic miR-103 inhibits endothelial proliferation by targeting IncWDR59
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Purpose: We test the hypothesis that Dicer impairs EC regeneration through miRNA-mediated suppression of miR-103, which increases the expression of lncWDR59 in ECs and thereby decreases EC proliferation.

Methods: In EC-Dicer-/- mice, Notch1 and β-catenin activation and EC proliferation were decreased by inhibiting Notch1 activity. This mechanism may contribute to the pro-atherogenic effects of Dicer.

Results: In EC-Dicer-/- mice, endothelial Notch1 and β-catenin activation and EC proliferation were increased in atherosclerotic arteries. The novel IncRNA WDR59 was the most significantly upregulated IncRNA in EC-Dicer-/- mice and its sequence contained a putative miR-103 binding site. Inhibition of miR-103 increased Notch1 and β-catenin activation and EC proliferation and apoptosis.

Conclusions: MiR-103 targets the novel IncRNA WDR59 in ECs and thereby impairs EC proliferation by inhibiting Notch1 activity. This mechanism may contribute to the pro-atherogenic effects of Dicer.

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Circulating long-noncoding RNA LIPCAR and left ventricular diastolic function in patients with uncomplicated type 2 diabetes mellitus
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Purpose: Our aim was to analyse LIPCAR as potential biomarker of early cardiac alterations in patients with well-controlled T2DM of short duration.

Methods: Forty-eight T2DM men with well-controlled T2DM of short duration and without structural heart disease or cardiac surgery were eligible. A complete panel of clinical, biochemical and metabolic characteristics was measured. Left ventricular (LV) dimensions and function were measured by magnetic resonance imaging (MRI). RNA was isolated from serum samples using miRNeasy kit. LIPCAR level was quantified using qRT-PCR.

Results: Univariate regression analysis indicated that LIPCAR was associated with parameters of LV diastolic function, including the peak filling rate of the early filling phase (E), the peak (E-decelerate) and mean (E-decelerate) deceleration gradients of A and mean the ratio E/A peak flow (P < 0.050 for all associations). There was no association between LIPCAR and parameters of LV dimensions or systolic function.

Conclusions: The level of serum LIPCAR is predictive of LV diastolic function in patients with uncomplicated T2DM and may be helpful in the evaluation of early cardiac alterations in T2DM.
Endothelial cell adenose deaminase action on RNA-1 is critically involved in vascular development and homeostasis in vivo

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Background: Adenose deaminase action on RNA-1 (ADAR1) binds to double-stranded RNAs and mediates adenose (A) to inosine (I) RNA editing, which is a widespread post-transcriptional mechanism in mammals that affects several coding and regulatory RNAs, by altering their sequence and structure. However, the role of ADAR1 in vascular system has not been reported so far.

Methods and Results: To investigate the role of ADAR1 in vascular development, ADAR1flox/flox mice were inbred with mice carrying a tamoxifen-inducible VE-Cadherin-Cre transgene (Cdh5-CreERT2) creating an inducible endothelial cell-restricted ADAR1 knockout model. ADAR1flox/flox mice were inbred with mice carrying a tamoxifen-inducible VE-Cadherin-Cre transgene (Cdh5-CreERT2) creating an inducible endothelial cell-restricted ADAR1 knockout model.

Conclusion: The RNA editor ADAR1 is critically involved in vascular development and homeostasis in vivo.

Sympathetic transmission in perivascular adipose tissue function in health and obesity

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Background & Aims: Healthy perivascular adipose tissue (PVAT) exerts an anti-contractile effect on resistance arteries which is vital in regulating arterial tone. Activation of β3-adrenergceptors by the neurotransmitter, noradrenaline, may be implicated in the anti-contractile effect of PVAT. In obesity the anti-contractile effect is lost, leading to the development of hypertension. Accordingly, we have investigated the effect of sympathetic nerve stimulation (SNS) within healthy and obese PVAT on the anti-contractile effect, and have identified the mechanisms involved.

Methods: Electrical field stimulation (EFS) profiles of healthy C57 mouse mesenteric arteries (<200μm, 4+PVAT) were characterised using wire myography (0.1-30Hz, 20V, 0.2ms pulse duration, 4s train duration). To demonstrate the release of an anti-contractile factor, the solution surrounding stimulated exogenous PVAT was transferred to a PVAT denuded vessel. Neural inhibition using tetrodotoxin (TTX, 1μM), or sympathetic denervation using 6-hydroxydopamine (6-OHDA, 2μM) were performed. β3-adrenecceptor function was investigated using the agonist CL-316,243 (10μM) and antagonist SR59203A (100μM). A model of obesity was set-up by feeding C57s a 60%-fat diet over a period of 10-12 weeks. EFS profiles of healthy arteries were compared to arteries from aged-matched obese mice, and the β3-adrenecceptor agonist CL-316,243 was tested.

Results: During EFS PVAT elicits a reproducible anti-contractile effect, which is replicated using exogenous PVAT. Solution transfer from stimulated exogenous PVAT to a -PVAT vessel significantly reduced contraction, confirming that stimulated PVAT releases a transferable anti-contractile factor. Neural inhibition using TTX, or sympathetic denervation with 6-OHDA, abolished all anti-contractile activity implicating sympathetic nerves in release of anti-contractile factors. β3-adrenecceptor agonist CL-316,243 enhanced the anti-contractile effect, and β3-adrenecceptor antagonist SR59203A reduced the anti-contractile effect. Complete inhibition of the effects of the solution transfer could be achieved by incubation of exogenous PVAT with SR59203A. In arteries from obese mice, the EFS-induced anti-contractile effect was lost, and could not be restored using CL-316,243.

Conclusions: These results demonstrate that SNS in PVAT elicits an anti-contractile effect by activation of adipocyte β3-adrenecceptors, triggering the release of vasodilators. In obesity, β3-adrenecceptors may have become desensitised, resulting in a loss of function, and leading to hypertension.

WITHDRAWN