Tryptophan-niacin metabolism regulates vascular inflammation via N1-methyl-4-pyridone-3-carboxamide (4PY)

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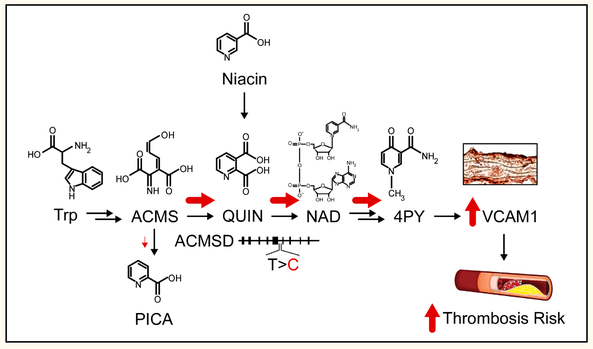
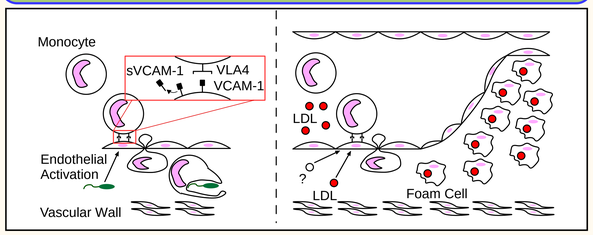
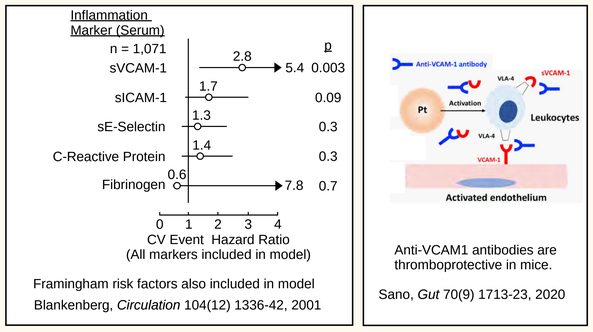
Abstract



Dietary tryptophan and niacin (vitamin B3) are converted to quinolinic acid (QUIN). Genetic variation in the gene encoding ACMS dehydrogenase (ACMSD) alters circulating 4PY levels, which in turn regulate vascular inflammation and cardiovascular risk via vascular cell adhesion molecule 1 (VCAM-1).

Background



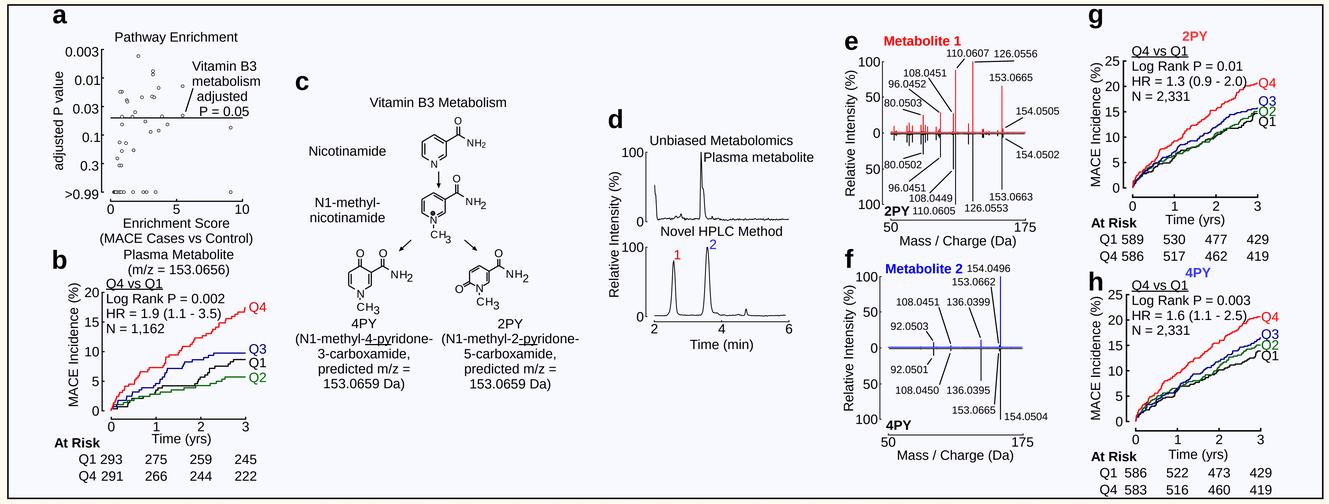


Anti-VCAM1 antibodies are thromboprotective in mice.

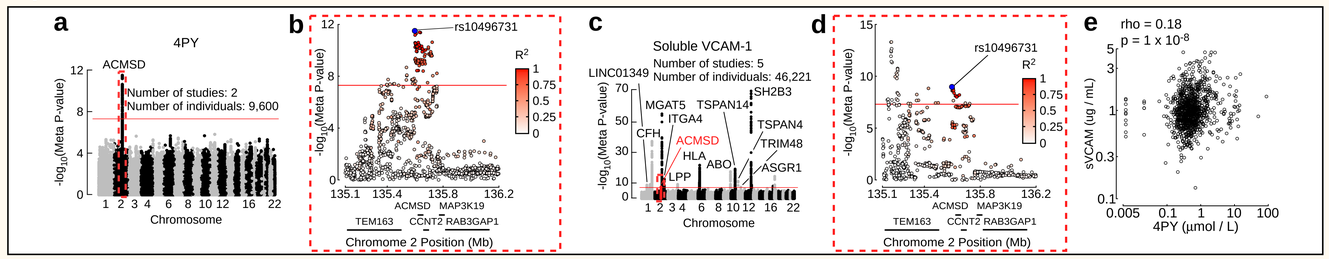
Sano, *Gut* 70(9) 1713-23, 2020

VCAM-1 is a vascular endothelium-specific surface protein that enables extravasation of monocytes in response to pro-inflammatory stimulus, including oxidized lipoproteins. A portion of expressed VCAM-1 is released as soluble VCAM-1 (sVCAM-1), a biomarker that predicts cardiovascular risk independently of systemic markers. VCAM-1 knockdown is protective against atherosclerosis and thrombosis in mice.

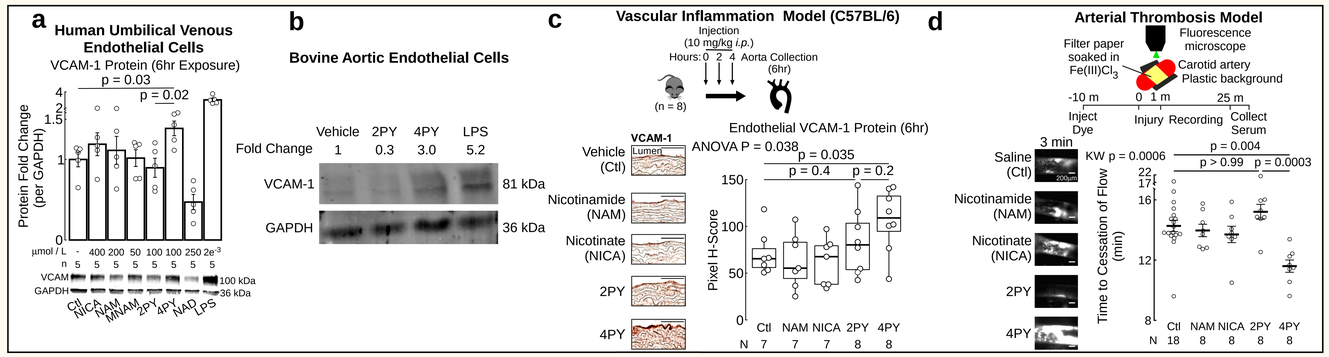
Results



4PY is independently associated with future CVD risk. Patients undergoing elective diagnostic catheterization were followed for three years. The primary endpoint was major cardiovascular event (MACE), defined as death, myocardial infarction, or stroke. (a) Unbiased metabolomics revealed the niacin (vitamin B3) metabolism pathway and one of its intermediates (b) were associated with future events. (c) this intermediate could be 2PY or 4PY. (d) A novel HPLC method reveals two chromatographic peaks with MS-MS fragmentation spectra identical to (e) 2PY and (f) 4PY. (g-h) A validation study using a novel LC-MS-MS method in a separate clinical cohort revealed 4PY is associated with risk. Hazard ratios (HR) adjusted for established risk factors, CRP, and renal function.



ACMSD is associated with 4PY and sVCAM in humans. Meta-analysis of publicly available GWAS data. Manhattan plots of fixed effects P values are shown for (a) 4PY and (b) sVCAM-1. The lead SNP within ACMSD is shown within a 1 Mb region for (c) 4PY and (d) sVCAM-1, and linkage disequilibrium is shown in red. (e) In human serum, 4PY and sVCAM-1 were weakly correlated. Mb, millions of base pairs

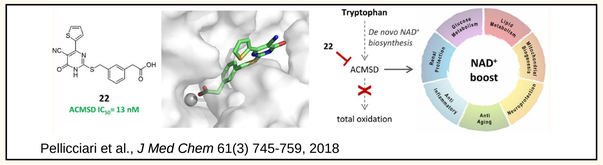


4PY enhances VCAM-1 expression and arterial thrombosis.
(a) Human and (b) bovine vascular endothelial cells were incubated with niacin metabolites for six hours, and 4PY elevated VCAM-1 expression. In mice, 4PY increased arterial VCAM-1 expression and accelerated arterial thrombosis.

Significance

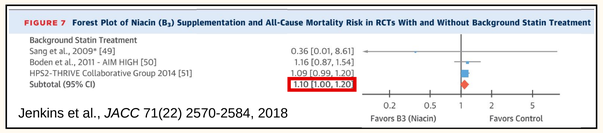


Supplemental niacin and NAD analogs may contribute to 4PY levels and cardiovascular risk. Fifty seven nations mandate niacin foritication in food, including the United States.



Pellicciari et al., *J Med Chem* 61(3) 745-759, 2018

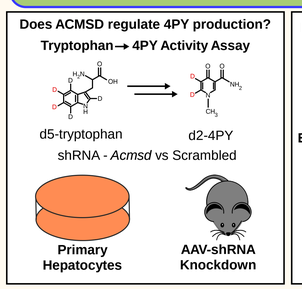
ACMSD inhibitors may elevate cardiovascular risk via 4PY production.



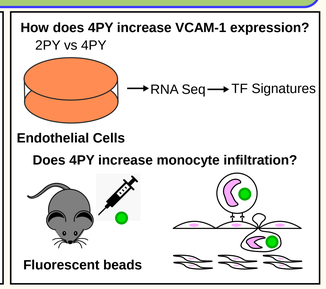
Jenkins et al., *JACC* 71(22) 2570-2584, 2018

4PY production from niacin may account for the failure of Niaspan (simvistatin/niacin/laropiprant) clinical trials.

Future



shRNA knockdown in mouse liver cells will test whether ACMSD regulates the conversion of tryptophan to 4PY.



RNA sequencing may elucidate the mechanism of 4PY-induced VCAM-1 expression. Increased VCAM-1 may induce monocyte infiltration.

Acknowledgements

Paul Fox Lab: HUVEC Isolation
Jennifer Buffa: Mouse aorta dissection
Maya Camhi: Mouse aorta sectioning
Jim Anderson: 2PY and 4PY synthesis

This work is supported by:
P01 HL147823-02
T32 HL134622-04
T32 GM007250-46