

Poster Presentation

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Vanin-1- a human ectoenzyme involved in inflammation, metabolism and disease

T. Peat¹, Y. Boersma¹, J. Newman¹, T. Adams¹, G. Krippner², K. Bozaoglu²

¹CSIRO, Biosciences Program, Parkville, Australia, ²Baker IDI Heart and Diabetes Institute, Melbourne, Australia

Inflammation is steadily gaining recognition as contributing to different disease states, e.g. cancer, immune dysfunction and cardiovascular disease. Vanin-1, a GPI-anchored, developmentally regulated member of the nitrilase family, sits at the intersection of many known pathways of inflammation. Three members of the vanin family of enzymes in humans have been described, with vanin-1 and vanin-2 having confirmed enzymatic activity. A known substrate is pantetheine which is hydrolyzed to give vitamin B5 and cysteamine. One function of these enzymes is in pantothenate recycling, and therefore they are involved in the Coenzyme A cycle and metabolism. Mouse knockout studies have shown that Vnn1(-/-) mice are resistant to oxidative stress, intestinal inflammation and colitis. Epidemiological studies have shown that mutations in vanin-1 in humans are associated with child obesity¹; other studies show an association with cholesterol homeostasis and cardiovascular disease. Importantly, the metabolic pathways of lipid metabolism and inflammation are interconnected² whereby impairment of lipid metabolism leads to inflammation and inflammation leads to impairment of lipid metabolism. We recently solved the structure of a soluble form of human vanin-1 using a single heavy atom derivative and anomalous scattering to 2.3 Å resolution. It has two domains: a predicted nitrilase domain and a cap domain which has no known sequence homology to any other structural domain. We also have structures with inhibitors bound and have performed mutational studies to determine the function of the cap domain and affirm the catalytic residues in the catalytic site. Structural studies have been complemented by enzymatic assays showing various levels of activity for the mutant and wild type enzymes. These data will be fundamental in characterizing vanin-1 in different disease states.

[1] Jacobo-Albavera, P.I. Aguayo-de la Rosa, T. Villarreal-Molina et al., *PLoS ONE*, 2012, 7:e49818, [2] M.L. Fitzgerald, Z. Mujawar, N. Tamehiro, *Atherosclerosis*, 2010, 211: 361-370

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