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Title: Host exfoliome responses to a dietary lignan intervention in the context of enterolactone excretion phenotype

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High-fiber plant foods contain lignans that produce bioactive enterolignans, enterolactone (ENL) and enterodiol (END). Reduced colon tumorigenesis in animal models and lower colorectal cancer risk in humans have been associated with enterolignan exposure. To gain mechanistic insight into the chemoprotective effects of lignans in humans, we conducted an NIH UO1 dietary supplement study where flaxseed lignan supplement (50 mg/d secoisolariciresinol diglucoside) compared to placebo was assessed with respect to host gene expression in colon biopsies and fecal exfoliated colonocyte RNA (exfoliome). Forty-two healthy men and women (20-45 y) were enrolled into a 2-period 60 day randomized, crossover intervention and data were subsequently analyzed for differences in host exfoliome gene expression. RNA-seq was used to measure differentially expressed (DE) genes in colonic mucosa and exfoliated cells, and the DE genes were subjected to a functional analysis using Ingenuity Pathway Analysis. This resulted in the detection of 279 DE genes (FDR<0.05) in subjects with the high-ENL excretion phenotype and 957 DE genes (FDR<0.05) in those with the low-ENL excretion phenotype, in response to lignan supplement compared to placebo. Analysis in exfoliated cells suggested that low-ENL excreters may be predisposed to proinflammatory cellular events due to upregulation of NFκB, and an

inhibition of the PPARγ network. These results suggest that individuals with high-ENL phenotypes could benefit from dietary lignan intervention as a chemoprevention strategy.