# SPECIFIC EFFECTS OF 9- AND 13- HYDROXYOCTADECADIENOIC ACIDS (9- AND 13- HODES) ON HUMAN MONOCYTE ACTIVATION AND MACROPHAGE DIFFERENTIATION.

**V. Vangaveti & R,L. Kennedy**
*Department of Medicine, School of Medicine and Dentistry, James Cook University, Townsville, Queensland, Australia*

In diabetes, activation of monocytes, macrophage differentiation in arterial walls, and foam cell formation are increased contributing to macrovascular complications. Mechanisms regulating these processes are incompletely understood. HODEs are oxidised linoleic acid (LA) derivatives produced non-enzymatically from LDL (oxLDL) or by enzyme 15-lipoxygenase. 9-HODE, (n-6) is pro-inflammatory and may act through the GPR132 receptor, while 13-HODE, (n-7), may have protective effects similar to palmitoleate (also n-7). We studied effects of long chain fatty acids (LCFA) HODEs, LA and α-linolenic acid (C18, n-3, ALA) on differentiation and gene expression in THP-1 cells.

Monocytes were fully differentiated into macrophages with 100nM phorbol myristate acetate (PMA), while 1 nM PMA synergized with 30 µM LCFAs increased expression of activation marker CD11b, macrophage morphology and lipid accumulation (oil red-O). Monocyte cell number was decreased by HODEs ($p < 0.001$) but not LA or ALA. Decreased cell viability was confirmed, and shown to be due to apoptosis (caspase 3/7 activation) rather than cytotoxicity. Monocyte activation (PMA 100 nM or PMA 1nM + 30µM HODEs) markedly increased expression of lipogenic genes FABP4 and PPARγ. Genes involved in reverse cholesterol transport (ABCA1 and SCRB) were activated by HODEs. These effects were not seen to be induced by ALA and LA. Stearoyl CoA desaturase, increased in insulin resistance, was decreased in monocytes by 13-HODE, but increased during activation and in macrophages by 9-HODE. 9-HODE specifically increased foam cells (lipid droplets) in differentiated macrophage cultures. Possible mediators of fatty acid effects include long-chain fatty acid receptors (GPR120 and GPR132) and PPARγ. GPR120 was predominantly expressed in monocytes and GPR132 in macrophages (PCR and immuno-histochemistry) with 9-HODE increasing GPR132 expression. A decrease in expression of GPR120 and an increase in GPR132 was observed when treated with HODEs synergized with 1nM PMA.

9- and 13-HODE have specific effects on monocyte activation, macrophage differentiation, lipid transport and signaling genes compared to LA and ALA. Ongoing work with receptor

activators/inhibitors and gene silencing will clarify which signaling pathways are involved in the actions of long-chain fatty acid mediators.