

Janice Drew's work on diet and cancer

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Abstract

Obesity and associated reduced consumption of plant derived foods are linked to increased risk of colon cancer as well as a number of other organ specific cancers. Inflammatory processes are a contributing factor but the precise mechanisms remain elusive. Obesity and cancer incidence are increasing worldwide, presenting bleak prospects for reducing, or preventing, obesity related cancers. The incidence of these preventable cancers can be achieved with greater understanding of the molecular mechanisms linking diet and carcinogenesis. Janice Drew has developed a research program over recent years to investigate molecular mechanisms related to consumption of anti-inflammatory metabolites generated from consumption of plant based diets, the impact of high fat diets and associated altered metabolism and obesity on regulation of colon inflammatory responses and processes regulating the colon epithelium. Comprehensive strategies have been developed incorporating transcriptomics, including the novel gene expression technology, the GenomeLab System and proteomics, together with biochemical analyses of plasma and tissue samples to assess correlated changes in oxidative stress, inflammation and pathology. The approaches developed have achieved success in establishing antioxidant and anti-inflammatory activity of dietary antioxi-



Figure 1 Dr. Janice Drew, PhD, Rowett Institute of Nutrition and Health, University of Aberdeen, Greenburn Road, Bucksburn, Aberdeen, AB21 9SB, United Kingdom.

dants and associated genes and pathways that interact to modulate redox status in the colon. Cellular processes and genes altered in response to obesity and high fat diets have provided evidence of molecular mechanisms that are implicated in obesity related cancer.

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INTRODUCTION AND EDUCATIONAL EXPERIENCE

Dr. Janice Drew is a Senior Research Fellow in the Rowett Institute of Nutrition and Health within the College of

Life Sciences and Medicine at the University of Aberdeen (Figure 1). She received her BSc Hons (First Class) degree in Horticulture from the University of Strathclyde (Glasgow, UK) in 1991. Her honors project involved investigation of bioactivities of phytochemicals produced from genetically transformed root cultures. She pursued graduate work at the University of Durham (UK) and received her PhD in plant molecular biology in 1994. Subsequently, Dr. Drew trained as a postdoctoral fellow in molecular neuroendocrinology, investigating G protein coupled receptor signalling in circadian rhythms and appetite and energy balance, with Professor Morgan at the Rowett Research Institute (Aberdeen, UK), supported by a Strategic Alliance with Servier (France). Dr. Drew has been an invited speaker at international meetings and is a peer reviewer and editor for scientific journals, guest editing a recent special issue entitled Obesity Cancer Links^[1]. Dr. Drew peer reviews grants for international funding agencies and has recently developed a new MSc Molecular Nutrition program at the University of Aberdeen. On the basis of her achievements as an independent investigator she received a promotion firstly in 2000 and again in 2007 and was also awarded for individual performance in 2005.

ACADEMIC STRATEGIES AND GOALS

Over recent years, Dr. Drew has developed a research program investigating links with diet and colon cancer. Hereditary links to colorectal cancer development are well established but the majority of cases are sporadic with little or no evidence of hereditary factors. Inflammation and obesity are increasingly emerging as factors significantly increasing colon cancer risk as well as a number of other organ specific cancers. Plant-derived sources of anti-inflammatory compounds and reduced calorie consumption may be significant factors modulating the life-time risk of developing colorectal cancer. Currently Dr. Drew is investigating the molecular and cellular effects of high fat diets and associated obesity with colon pathology and modulation by anti-inflammatory plant-derived components. A systems approach incorporating genomic, proteomic, biochemical and physiological analysis is applied to identify molecular mechanisms linking obesity and consumption of dietary plant phenolics with regulation of genes and proteins involved in key processes such as, proliferation, differentiation and apoptosis, inflammation and adipokine and endocannabinoid signalling using *in vitro* cell and human colon explant cultures, *in vivo* models and human colon tissues. Dr. Drew's research has contributed to evidence of molecular mechanisms linking anti-inflammatory gut metabolites and diet-induced obesity with colon cancer (Figure 2).

ACADEMIC ACHIEVEMENTS

The following contributions highlight Dr. Drew's activities in the field of diet and colon cancer.

Diet-induced oxidative stress in colon modulated by dietary phenolics

Dietary antioxidant deficiency was demonstrated to in-

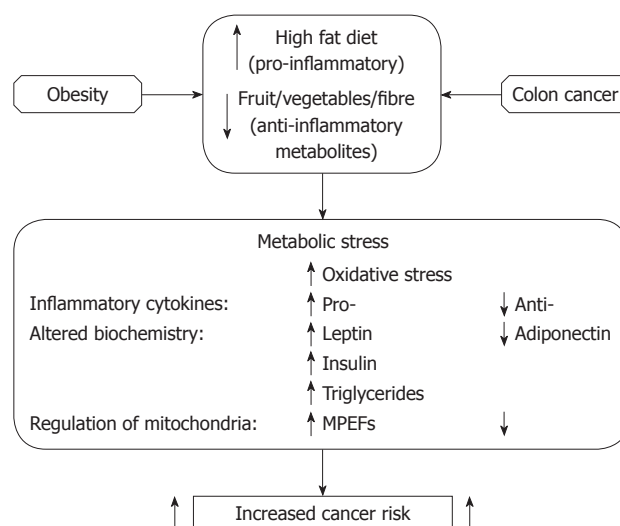


Figure 2 Obesity cancer links. Obesity and colon cancer are both associated with increased consumption of diets rich in saturated fats, together with reduced consumption of fruit, vegetables and fibre. Consumption of high fat diets and diets deficient in fruit, vegetables and fibre promotes metabolic stress. This is manifested by increased oxidative stress and inflammatory responses, altered levels of adipokines, insulin and triglycerides and changes in protein profiles of mitochondrial multiple protein expression forms (MPEFs). Research investigating the metabolic changes associated with obesity is elucidating molecular mechanisms linked to associated increased cancer risk.

crease oxidative stress and inflammatory prostaglandins in colon tissues^[2]. Anti-inflammatory plant derived gut metabolites have the potential to alleviate oxidative stress in gut tissue^[2,3]. Supplementation of antioxidant deficient diets with salicylic acid, a plant phenolic, was found to reduce oxidative stress and inflammatory prostaglandins with an associated increase in glutathione peroxidase activity^[2]. Glutathione peroxidases (Gpx) are important moderators of oxidative stress that is implicated in the pathogenesis of numerous diseases including colon cancer^[4]. Novel sites of glutathione peroxidase expression in colon were identified^[5]. Both cytosolic isoforms, Gpx1 and Gpx2 were observed in lymphatic tissue. Only Gpx2 was expressed by luminal colon epithelium, implying a specific role in regulating oxidative stress in the gut epithelium^[5]. These studies have made a significant contribution to research on the role of Gpx in regulation of the colon epithelium^[6]. The ability of plant phenolics to modulate antioxidant enzymes and inflammatory prostaglandins in colon tissue^[2,3] and cells^[7,8] may be an important mechanism in inhibiting colon cancer development. The studies outlined above have contributed to establishing antioxidant activity of salicylates in cells and tissues^[9-12] and citation in reviews on the role of salicylates in cancer prevention^[13].

Protein expression profiling in colon in response to pathology and diet

Proteomic approaches have been applied linking precancerous changes, increased levels of inflammatory prostaglandins and oxidative stress with altered protein profiles in colon^[3,14]. A targeted organelle proteomic approach led to the first study profiling colon mitochondrial proteins^[15] and identification of altered mitochondrial protein pro-

files in colon associated with obesity^[16]. The importance of multiple protein expression forms was highlighted^[15]. Changes in multiple protein expression forms contribute significantly to changes in protein profiles in colon in responses to pathology^[14] and diet^[3,15,16]. Multiple protein expression forms of tropomyosin were associated with precancerous changes in colon and may be a significant factor in metabolic changes that result in the onset of colon pathology^[14]. These studies have contributed to development and application of research strategies and insights on gastrointestinal^[17] and mitochondrial^[18-20] proteins that have been highlighted in reviews of proteomic methodologies and tools to identify and develop biomarkers of colon pathology^[21-25].

Molecular mechanisms linking obesity with colon cancer

Insulin, leptin and adiponectin hormones are deregulated in obese individuals. Colon epithelial localisation of insulin, leptin and adiponectin hormone receptor gene expression^[26] indicated a role for these hormones in regulating the colon epithelium and potential links to obesity related colon cancer. High fat diets and associated obesity impact on signalling *via* these receptors with evidence of altered expression of protein profiles in colon mitochondria linked to energy metabolism, electron transport chain, redox regulation, protein synthesis, folding, degradation transport and calcium binding^[16,27]. Leptin was shown to up-regulate gene expression of inflammatory cytokines^[28] known to be increased in obese individuals^[29] and in colon cancer^[30]. Leptin was also shown to alter protein profiles in colon tissue linked to calcium binding, cell cycle, cell proliferation, electron transport chain, energy metabolism, protein folding and transport, redox regulation, structural proteins and proteins involved in transport and regulation of mucus production. Further studies highlighted that consumption of high fat diets that lead to obesity increase cancer risk. Consumption of high fat diets was associated with changes in leptin regulated processes and increased expression of the colon stem cell marker *Lgr5* (unpublished observations). The studies have made significant progress in establishing and supporting a role for adipokine hormones in regulating colon homeostasis and links with obesity related colon cancer^[16,26-28]. Consequently this work has been highlighted in recent studies dissecting the complex associations linking obesity and colon pathology^[31-34] and reviews presenting new insights on obesity cancer links^[35].

Validation and application of novel custom designed gene expression technology to study colon pathology

The GenomeLab Genetic Analysis System presents a novel technology platform for quantitative multiplexed gene expression analysis^[36]. This system permits custom design options for relative quantification of multiple gene target expression simultaneously in a single reaction, using nanogram quantities of total RNA template. A custom designed GeXP assay of inflammatory cytokines showing altered regulation in human colon normal, polyp and

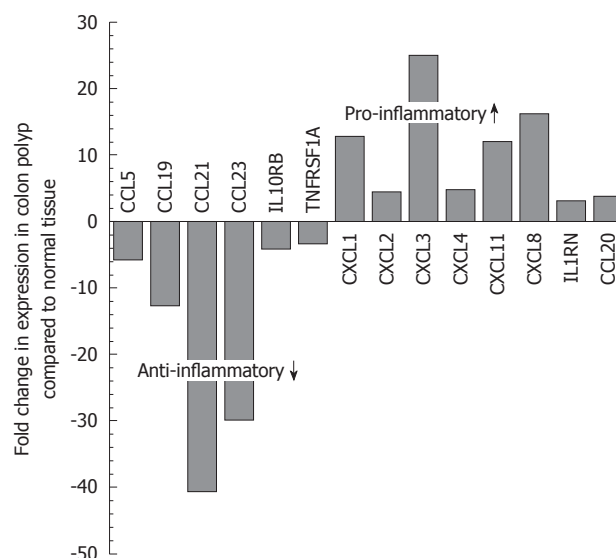


Figure 3 Application of a custom designed multiplex of inflammatory cytokines associated with early events in colon carcinogenesis. GeXP profiling generates gene expression signatures to reveal molecular characteristics associated with pathology. GeXP facilitates a rapid analysis of multiple gene targets simultaneously and is feasible for analysis of small tissue biopsy samples (either fresh or frozen archived tissues) available from clinical specimens since only nanogram quantities of total RNA are required. Custom designed multiplex GeXP assays present opportunities to conduct gene regulatory studies in response to dietary metabolites and links with pathology. Studies in our lab are focused on clinical applications of novel custom designed assays to identify signature gene expression profiles and biomarkers of dysplasia, identification of novel disease sub-types and responses to dietary intervention and therapeutics.

tumor tissues has been validated in comparisons with macroarray and single-plex real-time PCR assays^[36]. GeXP assays facilitate characterisation of gene expression signatures associated with responses to diet, hormone signalling, therapeutics and/or pathology (Figure 3). Novel custom designed GeXP assays are currently being developed and applied in our clinical, diagnostic and regulatory studies of multiple gene targets linked to colon pathology.

CONCLUSION

Identification of the genes and proteins altered in response to obesity and carcinogenesis is a crucial first step in elucidating mechanisms associated with obesity related cancers. Application of comprehensive strategies in model systems has permitted elucidation of inflammatory pathways and cellular processes that are implicated in obesity related cancer and anti-inflammatory dietary metabolites that may be useful in ameliorating the detrimental impact of high fat diets. An understanding of the cellular processes that are altered with consumption of high-fat diets and modulatory effects of consuming plant based diets will assist in developing strategies to reduce these preventable cancers.

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