Researcher Profile

UHN Microarray Centre

Dr. Michael Archer

Identifying genes and dietary factors involved in carcinogenesis

One aspect of Dr. Archer's research programme is to understand the genetic basis for the differences in susceptibility to breast cancer induction of certain rat strains. Wistar-Furth (WF) rats develop multiple mammary adenocarcinomas following treatment with a mammary carcinogen, whereas Copenhagen (Cop) rats are completely resistant to the development of mammary tumours. Dr Archer and his colleague Dr Yaacov Ben-David from Sunnybrook Health Sciences Centre isolated cell lines from tumours induced in resistant Cop x WF F1 rats by infusion of a retrovirus harbouring v-Ha-ras directly into the main mammary ducts. Some of the cell lines were able to grow in soft agar but a significant number did not display anchorage-independent growth. They hypothesised that the anchorage-dependent and –independent cell lines may recapitulate the resistance and susceptibility of Cop and WF rats, respectively, to mammary carcinogenesis and could facilitate the identification of breast cancer susceptibility genes. Using the UHNMAC Gene Expression Service (Agilent platform), genes that are differentially expressed in these cell lines were identified (1). The expression of IL-24 and β4 integrin was highly correlated with the inability of cells to grow in soft agar. Ectopic expression of IL-24 in anchorage-independent cells inhibited their growth in monolayer culture, in soft agar and in nude mice *in vivo*, and inhibited their ability to migrate and invade in *in vitro* assays. Furthermore, growth suppression by IL-24 was associated with the transcriptional up-regulation of $p27^{Kip1}$ via the activation of Stat3. They showed for the first time, that β4 integrin is a downstream target of IL-24. However, β4 does not play a direct role in regulating the proliferative capacity the rat mammary tumour cells. Overall, their results show that IL-24 suppresses the growth of rat mammary carcinoma cells and may play a role in the resistance of Cop rats to mammary carcinogenesis.

A Professor in the Departments of Nutritional Sciences and Medical Biophysics at the University of Toronto, Dr. Archer also investigates the molecular targets of dietary factors involved in the development of breast and colon cancer. He has published a number of studies that focus on the role of fatty acid synthase (FAS) in tumour development. Most recently, he has shown that the transcription factor Sp1 regulates both *de novo* lipogenesis and proliferation in cancer cells, and he has proposed the concept that Sp1 coordinately regulates multiple biological processes that are essential for the survival, growth and progression of cancer cells (2). He has also recently shown that FAS is over-expressed in aberrant crypt foci, the earliest identifiable lesions in colon cancer development (3). Finally, in a series of studies in knock-out and mutant mice, Dr. Archer and his group have unraveled the complex interactions linking obesity, type II diabetes and colorectal cancer. He has shown that insulin and IGF-I are the key factors (4).

References

1. Xuan *et al.* Interleukin-24 Induces Expression of β4 Integrin but Suppresses Anchorage-Independent Growth of Rat Mammary Tumor Cells by a Mechanism That Is Independent of β4. Mol Cancer Res 2009,7:433
2. Lu & Archer. Sp1 coordinately regulates de novo lipogenesis and proliferation in cancer cells. Int J Cancer 2009 Jul 20 [epub ahead of print]
3. Lau & Archer. Fatty acid synthase is over-expressed in large aberrant crypt foci in rats treated with azoxymethane. Int J Cancer 2009, 124:2750
4. Ealey & Archer. Colon carcinogenesis in liver-specific IGF-I deficient (LID) mice. Int J Cancer 2008, 122:472

UHN Microarray Centre is a Certified Service Provider for the Agilent microarray and genomics platform. The centre also offers bioinformatics services, from experimental design to downstream data analysis and mining, enabling researchers to maximise the success of their genomics projects.