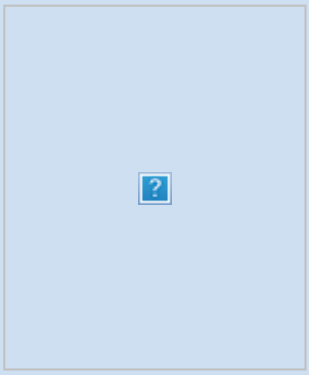
January 2010

Cancer: Parallel Studies Change Current Understanding of Gene Function



E2fs—a family of transcription factors responsible for helping turn genes 'on'—play central roles in controlling cell division, survival, and cancer. They can drive cell division and, if inappropriately activated, may trigger cell death, a protective mechanism against cancer development. Recent findings published in *Nature* co-led by TWRI's Dr. Rod Bremner turn two widely held notions—that E2fs are essential for division and can drive cell death—upside down.

Dr. Bremner speculates that, "Although cells can divide without E2fs they dislike doing so, perhaps because they don't have all the right equipment to copy their genetic information properly." Indeed, in the retina and other tissues, loss of E2f induced an increase in DNA damage.

Parallel studies with collaborator Dr. Gustavo Leone showed that activating E2fs are not required for cell division in multiple tissues in vivo, but that they are essential for cell survival. Dr. Bremner's lab focused on the developing retina and defined mechanisms to explain these phenomena. First, they showed that an unrelated protein family (Myc) promoted division in the absence of E2fs. Second, they discovered that E2fs promoted survival because they maintained levels of a protein called Sirt1. In cells without E2f, Sirt1 protein levels dropped and activated the p53 protein responsible for promoting cell death.

"Cancer cells often have high Myc levels, and combining that with low E2f could help these cells to divide and to induce mutations to escape natural and pharmaceutical attack. Understanding the effect of different combinations of Myc and E2f activity is important to define how best to treat different cancers."

Chen D, Pacal M, Wenzel P, Knoepfler PS, Leone G, Bremner R. Nature. 2009 Dec 17;462(7275):925-9. [Pubmed abstract]. *Research supported by Canadian Institutes of Health Research.*

Chong JL, Wenzel PL, Sáenz-Robles MT, Nair V, Ferrey A, Hagan JP, Gomez YM, Sharma N, Chen HZ, Ouseph M, Wang SH, Trikha P, Culp B, Mezache L, Winton DJ, Sansom OJ, Chen D, Bremner R, Cantalupo PG, Robinson ML, Pipas JM, Leone G. Nature. 2009 Dec 17;462(7275):930-4. [Pubmed abstract]. *Research supported by the National Institutes of Health.*

Leukemia: Discovering a New Population of Cells

The human blood system—in particular the hematopoietic stem cell (HSC) or blood stem cell—has been extensively studied; however, the exact

TGRI Researcher Awarded CFI Funds

TGRI's Dr. Shannon Dunn was awarded infrastructure funds in the latest round of the Canada Foundation for Innovation's (CFI) Leaders Opportunity Fund. The award will go towards supporting Dr. Dunn's research into PPARalpha as a mediator of sex differences in autoimmunity.

In total, this latest round of funding provided 83 projects across the country with approximately $14.8M in infrastructure support.

Congratulations Dr. Dunn!

Mark Your Calendar! Microarray Centre Symposium

On June 14, 2010, the UHN Microarray Centre will be hosting the "Functional Genomics: Present & Future" one-day symposium in the MaRS auditorium. Official event registration begins March 1, 2010.

The event will run from 8:30 AM until 5 PM and will include ten presentations on topics ranging from clinical applications of array-based technology to new research technologies available such as nanostrings and the nCounter system.

For more information on the symposium and how to register, visit www.microarrays.ca/info/symposium

mechanics behind how an HSC undergoes self-renewal remains unclear. Self-renewal is the process by which an HSC grows and divides to create an exact replica of itself, as well as cells different from itself (i.e. one or more specific types of blood cells that cannot renew).

"It's important that we understand the mechanics behind self-renewal because it's responsible for the life-long maintenance of the human blood system," explains OCI study-lead Dr. Norman Iscove.

His recent study findings identified a new population of HSCs, known as 'intermediate term' cells that persisted for a period of 6-8 months before becoming extinct or losing their ability to self-renew. The team used a mouse model and genetic approach to their investigations that have provided important information towards our understanding of stem cells.

"It is important for investigators to be able to distinguish between the different types of cells in the blood system," explains Dr. Iscove. "We need to be able to separate short-, intermediate- and long-term cells from one another so that HSC studies examine those cells capable of maintaining the blood system which is critically important for stem cell transplantation."

Patricia Benveniste, Catherine Frelin, Salima Janmohamed, Mary Barbara, Robert Herrington, Deborah Hyam, Norman N. Iscove. Cell Stem Cell 8 January 2010; 6(1):48-58 [epub ahead]. [Pubmed abstract]. *Research supported by the Terry Fox Foundation, the Canadian Institutes of Health Research, the Stem Cell Network, the National Institutes of Health, and the McEwen Centre for Regenerative Medicine.*

Cancer Biology: Learning to Sensitize 'Tenacious' Tumour Cells

Researchers at OCI have discovered a new pathway that tumours use to survive during conditions of hypoxia (deprivation of oxygen) and become more aggressive and resistant to current cancer treatment strategies. By strategically manipulating this pathway, researchers believe that these once 'treatment resistant' tumours could become sensitive to radiation or chemotherapy.

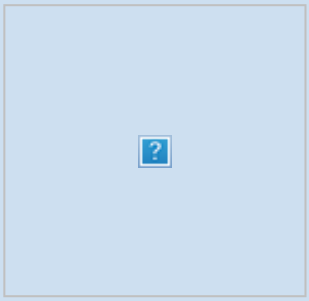
As explained by study lead Dr. Bradly Wouters, "It is extremely important to understand how to tumours are able to adapt to metabolic stresses like hypoxia because these mechanisms lead to more aggressive cancers that are difficult to treat effectively."

With colleagues from the Ontario Institute for Cancer Research and Europe, the team conducted a series of molecular investigations in several human cancers to show that the unfolded protein response (UPR) mechanism protects human tumour cells by enhancing the activity of *MAP1LC3B* and *ATG5* genes. This enables the tumour cells to carry out a form of self-eating or autophagy, thus allowing them to survive under nutrient and oxygen poor conditions. Ultimately, this activity promotes human tumour cell survival and contributes to tumour cell treatment resistance.

"When we disabled this adaptive mechanism through genetic or pharmacological agents, previously resistant tumours became less hypoxic and more sensitive to irradiation," comments Dr. Wouters. "Our future studies will continue to target the UPR as a mediator of hypoxic tumour environments to make resistant hypoxic tumour cells sensitive to treatment."

Rouschop KM, van den Beucken T, Dubois L, Niessen H, Bussink J, Savelkouls K, Keulers T, Mujcic H, Landuyt W, Voncken JW, Lambin P, van der Kogel AJ, Koritzinsky M, Wouters BG. J Clin Invest. 2009 Dec 14. pii: 40027. doi: 10.1172/JCI40027. [Epub ahead of print]. [Pubmed abstract]. *Research supported by the Dutch Science Organization, the Dutch Cancer Society, and the European Union Sixth Framework Programme.*

Neurology: Detailing the Process of Memory



The hippocampus is a region of the brain critical for establishing and retrieving long-term memories. A hotly debated topic in cognitive neuroscience is whether the hippocampus codes for memory strength (and is therefore mainly active for strong memories) or recollective experience (activity relates to retrieval of contextual information) during recognition. Thanks in part to findings from a TWRI-led study, this debate may finally be put to rest.

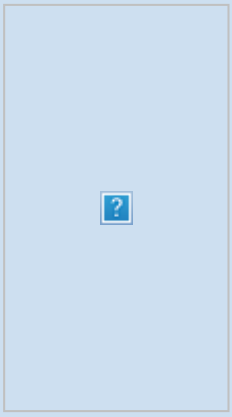
The study was led by Dr. Melanie Cohn in Dr. Mary Pat McAndrews' lab. Participants were asked to study pairs of words (A-B). The team then used functional magnetic resonance imaging (fMRI) to assess hippocampal activity while participants performed a recognition task for the first member of the pairs (A) presented alone and then in the presence of their pair member (A-B). They asked participants to rate the degree of strength or familiarity of A words (i.e., certain-new to certain-old) and whether they were able to recollect the original study experience. Importantly, while other areas of the brain showed increased activation in relation to memory strength, activity in the hippocampus only increased when context was recollected.

Drs. Cohn and McAndrews explain, "Things can seem very familiar at first but you may not be sure why (missing context). Suddenly everything 'makes sense' because information becomes recollected with the right context and you now know why something is familiar to you. The hippocampus seems to be critical to this 'conversion' of one type of memory experience to the other."

Cohn M, Moscovitch M, Lahat A, McAndrews MP. Proc Natl Acad Sci U S A.. [Epub ahead of print]. [Pubmed abstract]. *Research supported by the Canadian Institutes of Health Research.*

Cardiology: Re-Examining the Protective Properties of Beta-Blockers

The beta-blocker class of drugs is commonly prescribed to manage various conditions including arrhythmias, hypertension and following heart attacks. Beta-blockers are also recommended by the American Heart Association to decrease the occurrence of heart attacks around the time of surgery. Recent findings from a TGRI-led study are providing new insights into the differences that patients either prescribed or not prescribed beta-blockers experience during the perioperative period which includes pre-surgery, surgery and post-surgery.



Dr. Scott Beattie and colleagues Drs. Dumina Wijeysundera, Keyvan Karkouti, and Stuart McCluskey reviewed records from more than 4,000 noncardiac, nontransplant surgical patients who were at low risk for cardiac complication. Their findings showed that patients who were taking beta-blockers at the time of surgery had a history of hypertension, diabetes, renal failure, coronary artery disease, peripheral vascular disease, and congestive heart failure more often than those patients who were not taking beta-blockers. After adjusting for these pre-operative differences using a statistical tool called propensity score matching they found heart attacks occurred more frequently in patients who were on beta-blockers.

As explained by Dr. Beattie, "What is new and important in these findings is that major cardiac complications and mortality were increased for those patients prescribed beta-blockers who had more than a 35% drop in hemoglobin concentration"—an important finding for health care teams. Blood loss and acute anemia are very frequent occurrences in surgery. Until future studies can be conducted, it would be prudent to transfuse patients earlier than is currently recommended in patients taking beta blockers to avoid the 35% drop in hemoglobin. Our results here point to the need for a larger study."

Beattie WS, Wijeysundera DN, Karkouti K, McCluskey S, Tait G, Mitsakakis N, Hare GM. Anesthesiology. 2010 Jan;112(1):25-33.[Pubmed abstract].
Research supported by the R. Fraser Elliot Endowed Chair in Cardiac Anesthesia.