Hallmarks of Cancer Series – Hallmark 1

Genome Instability and Mutation

By Murray Junop

Cancer develops when a surprisingly large number of changes (mutations) occur in the genes in the cell. These changes are not the same in every cancer cell - to the point that essentially no two types of cancer are identical at the genetic level. Because of this diversity, efforts to understand the changes that cause cancer are challenging. Extensive research has shown there are common features (or hallmarks) shared among all types of cancers. These "hallmarks of cancer" include uncontrolled cell growth, spread of cancer cells from one location in the body to another, extended life of cancer cells, and the ability to make use of the immune system in abnormal, self-serving ways. Owing to their common occurrences in cancer, such hallmarks represent excellent targets for cancer treatment.

Cancer cells are infamous for their ability to change rapidly due to high rates of mutation and genetic instability (Hallmark 1). Consequently, treatments that work initially can fail in the long run due to further genetic changes that make chemotherapy less effective. With this in mind an obvious question becomes, why not focus on directly treating the cause of genetic change and instability?

In fact this approach is showing great promise and is considered by many researchers in the field to be the Achilles' heel of cancer. Dr. Murray Junop and his team of researchers, located in the Department of Biochemistry at Western University, are following this line of research - studying how preventing genetic instability can be used in combination with other types of cancer treatment to provide more effective methods of cancer therapy.

Every day each cell in the human body experiences hundreds of thousands of mutations. If left unrepaired, such mutations would rapidly alter the function of the genes that control normal cell growth and lead to cancer. Fortunately, we have dedicated sets of DNA repair genes that are able to manage the recognition and repair of cancer-causing mutations. These DNA repair genes act as first line guardians of the genome and are absolutely critical for prevention of cancer. Not surprisingly, people who inherit DNA repair genes with mutations that weaken their ability to work properly are prone to getting cancer. For example, some breast and colon cancers occur because of a genetically inherited faulty repair gene.

Most cancers are treated using radiation and/or chemotherapies that kill cancer cells by causing large amounts of DNA damage (mutations) within them. Cancer cells are thought to be selectively killed by such treatments due to their faster rates of DNA replication (cell division) and consequent inability to repair acquired mutations properly. Unfortunately, this approach has limitations because a few cancer cells can overcome DNA damage by boosting the activity of their own DNA repair genes. In this way, initially successful DNA damaging therapies are not effective due to acquired resistance in the form of a better ability to repair DNA damage.

The Junop Lab is tackling this problem by working to understand which genes are responsible for DNA repair and how this repair takes place. With this knowledge the researchers are seeking to design new drugs that target particular DNA repair gene functions that are known to prevent chemotherapy from killing cancer cells. Although in principle this seems straightforward, in practice the challenge is complex because of the large number of genes responsible for DNA damage repair. Current efforts in the Junop lab are aimed at understanding three different sets of repair genes responsible for repairing the most frequent forms of DNA damage. This research has already lead to important findings of the molecular workings of DNA repair that are necessary to exploit members of these repair systems for improved cancer therapies. In the long run the goal is to develop new drugs that will make cancer cells more likely to respond to currently available DNA damaging therapies.

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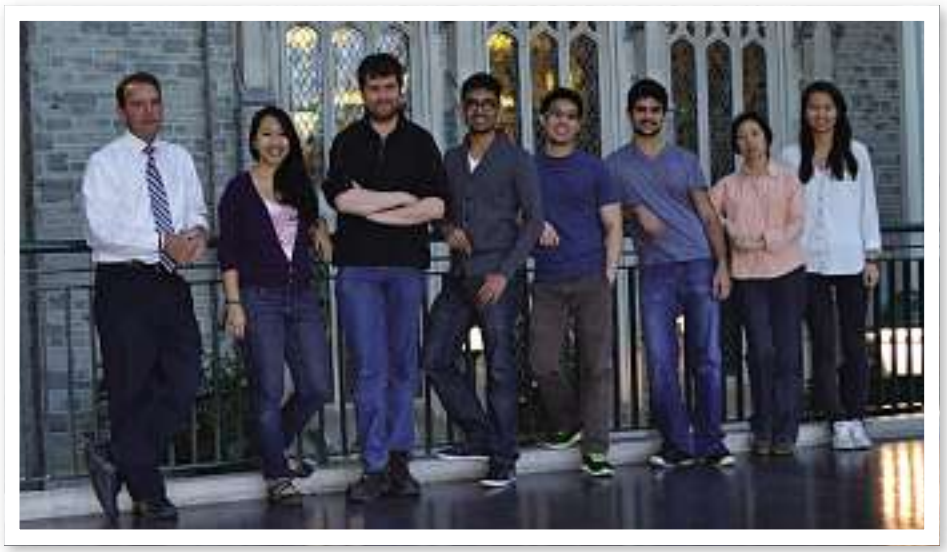

Junop Lab members from left to right: Murray Junop, Beverlee Buzon, Chris Brown, Khalid Hossain, Mac Mok, Hatim Kheir, Kun Zhang, Angela Zou