Cancer connections to hormones and growth factors

Professor Pomila Singh discusses the key motivations and components of her research on the role of Annexin A2 in the growth factor and co-carcinogenic effects of gastrin.

Could you explain why the roles of gastrin and Annexin A2 are so significant in colorectal cancers?

In a healthy body, cells with damaged DNA are either repaired or undergo cell death and are removed from the tissue so that a normal healthy cell can replace the dead cell. However, in the presence of elevated levels of PG, the damaged and perhaps mutated cells are rescued from cell death, which results in the accumulation of mutated cells which continue to grow and form tumours. Adding insult to injury, the tumour cells themselves begin to secrete PG, allowing further growth and progression of the cells to cancerous growths.

We learned that PG needs to bind to a molecule (ANXA2) on the surface of cells which facilitates entry of PG into cells and allows it to signal growth of the cells by activating several molecules.

How can dietary agents such as curcumin regulate the growth of such colorectal cancers?

Our laboratory is currently examining the mechanisms by which chemopreventive dietary agents, such as curcumin (a product of turmeric root, which gives the root its yellow colour and is used in many Asian curries), inhibit the growth effects of PG and ANXA2 on CRCs, and to determine if curcumin can be used in combination with other strategies we have developed to increase treatment potency against CRCs. Based on our studies so far, we have demonstrated that curcumin inhibits activation of a large number of molecules within the cancer cells in response to PG, resulting in the death of the cell.

Have you discerned any countries or populations who might have increased or reduced risks of colorectal cancers through diet?

Epidemiological studies have compared disease rates with dietary intake of specific populations inhabiting different parts of the world. It was learned that high dietary consumption of specific plant foods (such as turmeric, green tea, soy products) and calcium-containing foods (such as dairy products), along with consumption of relatively low levels of animal fats, results in lowering the risk for developing colorectal cancers.

South and East Asians generally consume diets rich in plant products containing one or more of the beneficial organic compounds, including curcumin, which may contribute to a lower incidence of CRCs in Asian countries compared to other parts of the world.

European countries with a high intake of wines, which are rich in a compound called resveratrol, are believed to be at a lower risk for heart diseases, and European populations with a high intake of dairy products containing high amounts of calcium apparently have lower incidence of CRCs compared to their neighbours.

What are the next steps in your research?

One of our objectives is to establish an in vitro laboratory-based cancer stem cell bioassay for measuring therapeutic efficacy of various naturally derived (such as curcumin) and synthetic chemotherapeutic drugs. Different formats of these assays are being developed in many different laboratories. We expect to apply for a patent for the bioassay we are developing in the near future.

While we are currently developing cancer stem cell bioassays using cultured cancer cells, the next step will be to develop methods for preparation of cancer stem cells from a patients tumour, which will require collaboration with other laboratories and physicians before our bioassay can move towards clinical trials. Personalised medicine for treating a patient's tumour, using this and many other strategies currently under development, is likely to become a reality within the next decade.
Colorectal cancer

Collaborative research at the utmbHealth is investigating the potential of hormones and molecules in the body which could be used as diagnostic biomarkers or as possible targets for treatment of cancer.

COLORECTAL CANCER, ALSO called colon cancer or CRC, develops in the colon, rectum and appendix, and is the third leading cause of cancer-related deaths in the Western world. Like many internal cancers, it can take many years to develop, and early detection greatly improves the chances of survival. Unfortunately, detection is often late as the prognosis can only usually be made when symptoms have already appeared.

Cancer researchers did however make a breakthrough in the early 1990s, when they found that colon cancer cells express relatively high levels of gastrin gene, which is not expressed by neighbouring normal colonic tissues.

Gastrin is a hormone that stimulates secretion of gastric acid by cells in the stomach, aiding gastric motility. In normal healthy individuals the gastrin gene is expressed only in the stomach by specific cells, called G cells, and this results in the formation of a mature peptide called amidated gastrin, or G17, which is secreted into the blood circulation and performs important functions in digestion and maintenance of the gut wall.

Colon cancer cells, unlike normal G cells, lack the machinery to make the mature G17 hormone from the gastrin gene. Instead, colon cancer cells mainly secrete immature or precursor forms of the hormone called progastrin (PG).

DELVING INTO PROGASTRIN

Professor Pomila Singh is a leading researcher at utmbHealth in the U.S. She and her colleagues used these findings and knocked down the expression of gastrin gene in colon cancer cells: which halted PG secretion. As Singh recalls, this finding was a major breakthrough: “The single step of knocking down gastrin gene expression in some colon cancer cells resulted in the loss of tumour formation by these cells, providing the first important insight regarding an important role of gastrin gene/progastrin in supporting the growth of colon cancer cells”.

The unexpected finding that gastrin gene and progastrin may play a critical role in the growth of some colorectal tumours which express the gene, led Singh and collaborators to develop methods of either targeting the expression of gastrin gene by cancer cells or inhibiting the action of progastrin.

Currently, her laboratory is investigating the molecular mechanisms by which progastrins and AnnexinA2 increase expression of stem cell markers in cancer cells, and the mechanisms by which chemopreventive dietary agents inhibit the expression of cancer stem cells.

PROGRASITN AND ANNEXIN A2

Studying the important role in facilitating initiation and progression of colorectal cancer, Singh and collaborators looked into the mechanisms by which PG signals cancer cells to continuously divide and grow. They found that AnnexinA2 (ANXA2) expressed on the surface of many cancer cells interacts with PG and facilitates its growth effects.

Singh summarises their findings: “Inhibiting the ability of PG to bind ANXA2 or inhibiting cells from expressing ANXA2, using different strategies developed by us, results in reducing growth and metastatic spread of tumours in mice”. The team therefore predicts that reducing the ability of PG to bind with ANXA2 or reducing the expression of PG and/or ANXA2 will be useful for inhibiting tumour growth in patients.

POMILA SINGH’S TEAM: I N ORTIZ, C KANTARA, DR S SARKAR, L K DOLORES AND C MAXWELL
ROLE OF ANNXININ-II IN GROWTH FACTOR/CO-CARCINOGENIC EFFECTS OF PROGASTRIN

OBJECTIVES
Currently the major objective of Dr Singh’s funded research is investigating molecular mechanisms by which gastrin and AnnexinA2 increase expression levels of stem cell markers in cancer cells. The team is also investigating mechanisms by which chemopreventive dietary agents such as curcumin inhibit expression of stem cell markers and thus reduce the growth of cancerous tumours. Translational aspects of their findings are being continuously developed, including establishing in vitro cancer stem cell bioassays for measuring therapeutic efficacy of various molecules, and developing biomarker assays for predicting the presence and staging of colorectal cancer disease in patients.

KEY COLLABORATORS
Dr Singh has worked with many influential colleagues over the years. Currently, the key lab personnel contributing to ongoing projects are:

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Dr Pomila Singh received her PhD degree from All India Institute of Medical Sciences, New Delhi, India in 1979 and moved to Medical College of Georgia, USA as a post-doctorate fellow with Dr Thomas Muldoon. For over 20 years, Dr Singh has been continually funded by the NIH to examine role of gastrin and progastrin and the IGF family of proteins in colon cancer. So far she has been awarded three patents, has submitted several additional patent applications for treating and diagnosing colon cancers, and has published 128 peer-reviewed papers to date. She has received several awards during her tenure and was named the Edna Seinsheimer Levin Professor of Cancer Studies in 2000.

In addition, the researchers found that circulating PG and ANXA2 may represent biomarkers of colorectal growths at early stages of the disease. The presence of these molecules in the blood of a patient post-treatment may represent an early sign of the return of the disease, thus it could be a way of avoiding expensive and invasive methods currently used for screening patients post-treatment.

DIAGNOSTIC MARKER
Assays, which measure the activity of a drug or biochemical in an organism, could be developed using the presence of specific molecules expressed in the blood of patients. These assays represent a relatively safe, non-invasive and inexpensive method that could be economically used to predict the presence and staging of cancer in patients. Yet, at present, such specific tests are not available for diagnosing the presence and stage of colorectal tumours.

Singh believes that their research may lead to this much-needed biomarker. “If our studies suggest that a specific range of PG and ANXA2 levels predict the presence and stage of CRC disease, it can be used as a screening tool in association with the currently used faecal test for predicting the presence of colonic tumours in a patient,” she explains. These biomarkers then would predict the presence of colorectal growths at relatively early stages so that a gastroenterologist could remove them by colonoscopy before they convert into cancerous forms.

NATURAL AGENTS
Another research area which Singh and her team are active in is natural agents. Many ancient cultural traditions have used herbal and dietary products for healing wounds and treating different diseases, including cancers. But until recently, the nature of the active compounds within herbal and dietary products remained largely unknown. With advances made in chemical purification of natural dietary products, it has been found that many roots, barks and leaves contain trace to significant amounts of active agents which appeared to have beneficial effects.

Some of these agents, such as curcumin, have brought renewed hope for finding a cure for cancer. "Laboratory tests soon demonstrated that many of the compounds extracted from plant products were effective in inhibiting the growth of cancer cells," points out Singh. "These relatively small compounds inhibited specific pathways, required by cancer cells to grow, and facilitated the death of the cells, but, surprisingly, these compounds spared the normal cells and appeared to be specifically toxic to cancer cells."

A challenge in this field is the fact that many of these dietary compounds taken orally, are poorly absorbed through the gut wall into the circulation, thus making it very difficult to achieve high enough concentrations for treatment purposes. While the use of these dietary compounds for treatment purposes continues to be a subject of intense research, Singh and her colleagues instead look at them as non-toxic alternatives to current treatments with harsh drugs. "A possible use of dietary compounds for preventing abnormal growth of cells in response to growth factors such as PG and ANXA2 will likely be a useful preventative strategy in the long run."

LOOKING FORWARD
With the help of structural biologists, Singh’s group are currently investigating the specific molecular domains of PG and ANXA2, which may lead to the development of small molecules that disrupt the interaction of PG and ANXA2 and thus inhibit the growth promoting effects of PG. Such a complex research project requires many researchers from different disciplines to work together. "Collaboration and a multidisciplinary approach have been critical for the progress we have made in our research and will remain a hallmark of all future research," she explains.

Recently, the team reported that PG and ANXA2 increase the number of stem cells which are required for repairing and replenishing normal tissues. Their results suggest that abnormal growth of stem cells in response to PG and ANXA2 may contribute to formation of colonic tumours. Singh and her colleagues are thus developing laboratory tests which can be used to examine the efficacy of toxic and non-toxic agents on the viability of cancer stem cells, so that a treatment, specific to the patient’s tumour can be developed to kill the seeds of cancerous growths.