Curbing carcinoma genesis

Exciting discoveries are uncovering the relationship between breastfeeding and breast cancer. Here, Dr Suhad Ali discusses how her research could help develop prognostic and therapeutic tools to suppress breast carcinogenesis.

What drew you to study the role of the prolactin (PRL) hormone and its signalling mechanisms in the normal development of the mammary gland and breast cancer?

As a biochemist, my interest in this field started with my PhD studies at McGill University, Montreal, Canada. I was interested in understanding how our body responds to hormones such as PRL at the cellular level and how these mechanisms change in pathological and disease conditions. This is a field of signal transduction. My interest continued during my postdoctoral training at the Max-Planck Institute of Biochemistry, Martinsried, Germany, and then as an independent investigator at McGill University.

Can you outline your research objectives to this end?

Our aim is to characterise the role of PRL in the normal functioning of the mammary gland,
as well as its role in breast cancer biology. Indeed, while PRL plays an important role in the mammary gland by controlling lactation, recent evidence from our group and others also suggests that the hormone acts as a critical regulator of breast cancer progression by suppressing early events in cancer metastasis. Ultimately, our aim is to develop PRL-based prognostic and therapeutic tools against breast cancer. Indeed, we plan to determine whether the PRL signalling pathways or its target genes can be used clinically for breast cancer prognosis and help improve treatment.

To what can the long-standing groundbreaking reputation of McGill University in the field of PRL research be attributed?

The contribution of Dr Henry Friesen who, in the early 1970s, purified and developed a radio-immunoassay to measure serum levels of PRL, was groundbreaking as until then it was thought that primates do not have PRL. Around 20 years later another groundbreaking discovery in the PRL field was made at McGill University, when Dr Paul Kelly’s laboratory, where I completed my doctoral studies, cloned the receptor for PRL.

Could you give an insight into the new concept in PRL regulation of breast carcinogenesis that you recently pioneered, and the results of these studies?

The lethal aspect of cancer becomes evident when it has spread from its primary location, such as the breast tissue, for example, to other sites within the body; this process is called metastasis. This is a complex process and is being investigated extensively by the scientific community. During disease progression, cancer cells acquire the ability to disseminate and eventually colonise other organs through certain molecular changes and processes. We found that PRL has the ability to suppress some key aspects of these mechanisms. In this manner, the hormone regulates the invasive capacity of cancer cells.

To date, the mechanism of lactation protection against breast cancer is not well understood and has been largely ignored. Why is this?

Studying lactation and PRL action as a means to combat breast cancer was largely ignored for many years as PRL was initially thought to promote tumour formation. It is only in recent years that this research path came to light, following our recent study unveiling this novel antitumourigenic role for PRL in breast cancer.

What are the potential benefits of enhancing understanding in this particular area?

At the molecular level, this protection against breast cancer is not fully characterised. We believe that our work characterising the role of PRL hormone in mammary differentiation and understanding the contribution of these mechanisms in breast cancer development and progression will help us, in part, to understand the protective role of breastfeeding against breast cancer.

Can more be done with a view to improving understanding of breastfeeding’s contribution to cancer development and progression?

Simply more research is needed in this area. By understanding how hormones and growth factors involved in lactation and breastfeeding impact the breast tissue at the cellular and molecular levels, we hope to discover new preventative mechanisms and use them to reduce the risk of breast cancer development. We also believe that it is important to have more public awareness that breastfeeding is not only beneficial for the infant but also for the mother. Indeed, breast cancer is a devastating illness and very costly to society. So we need to take every measure possible to reduce the risk of developing this disease.

THE MOST COMMONLY diagnosed cancer in women across the world is breast cancer. According to estimates provided by the World Health Organization (WHO), approximately 508,000 women died in 2011 alone as a result of this disease. Since the early 1990s, a correlation between prolactin (PRL) hormone and breast cancer has been presumed despite a lack of sound clinical data to support this. Traditionally thought to be a proocongenic growth factor, PRL plays a fundamental role in remodelling the breast tissue and enabling lactation and breastfeeding. With these morphological changes, mothers who breastfeed their children and do so on average for a sustained two-year period, are subject to an altered hormonal profile that is not shared by women who do not breastfeed.

While the debate surrounding a mother’s decision to breastfeed remains a sensitive issue regarding the benefits it may or may not have for a child’s development, there is far less public awareness around the effects of breastfeeding on mothers. With estimates from 2010 suggesting one in
In the same year, it was noted by the Society that lactation leads to a decreased risk of breast cancer in premenopausal women and that its apparent benefits mean breastfeeding should be encouraged, particularly among mothers who have already received treatment for breast cancer. However, a 2008 review in the Journal of Women's Health examining 31 studies of breastfeeding and its duration found it impossible to arrive at any consensus as to the purported benefits it confers upon mothers. The previously accepted notion that PRL is a progonocgeneic hormone has largely been responsible for this lack of clarity.

**MCGILL UNIVERSITY**

Leading McGill's groundbreaking research into PRL is Dr Suhad Ali, Associate Professor of Medicine at the Hormones and Cancer Research Unit, Haematology Division, and associate member of the McGill Cancer Centre. Her investigations into the relationship between growth factor signalling processes and cancer development have contributed significantly to the University's longstanding reputation for excellence in PRL research and resulted in a host of prestigious awards for Ali herself. In particular, Ali's attempts to characterise how key signalling pathways downstream of the PRL receptor lead to mammary epithelial cell differentiation, survival and carcinogenesis have led to her receiving several awards – National Cancer Institute of Canada Scientist Award, the Canadian Society for Endocrinology and Metabolism Young Investigator Award, as well as The Girls for the Cure: Breast Cancer Award, among others. With grants from the Canadian Institutes of Health Research (CIHR) currently extending to 2016, the exciting discoveries Ali's laboratory has made in determining novel mechanisms of breast carcinogenesis during her tenure at McGill may be just the beginning of an entirely new way of understanding breast cancer.

**ROLE REVERSAL**

At the start of the new millennium, studies began to appear which, while inconclusive, suggested a striking positive correlation between breastfeeding and reduced rates of breast cancer. In 2002, the Collaborative Group on Hormonal Factors in Breast Cancer reviewed 47 epidemiological studies that spanned 30 countries presenting data on over 50,000 women with breast cancer and almost 300,000 controls. Regardless of the differences between the countries' economic statuses, the sample groups’ ethnic origins, ages, menopausal statuses, number of children to each woman or their ages at the time of their first birth, there was little variance between the risk of developing breast cancer. The only significant factors appearing to affect breast carcinogenesis was whether a mother breastfed her baby and for how long. The study showed that for every 12 months of breastfeeding the relative risk of developing the disease decreased by 4.3 per cent, and with every birth this risk was further reduced by 7 per cent. This reassessment of the data has elicited a strong interpretation of the numbers; women who breastfeed for longer are less likely to develop breast cancer than women who do not.

In the same year, it was noted by the Society of Obstetricians and Gynaecologists of Canada that nine Canadian women developed breast cancer, researchers at McGill University in Montreal, Canada, are aiming to determine whether breastfeeding has any meaningful impact on such numbers. Following years of pioneering research at McGill into the role of PRL, a reassessment of this important hormone indicates a far more positive function than previously thought.

**DIFFERENTIATION HYPOTHESIS**

It is the terminal differentiation of mammary epithelial cells that occurs with alveologenesis that first provided clues to a molecular link between PRL and protection against breast cancer. Cancers develop not only as a result of defects in cell proliferation but also because of defects in differentiation. "We hypothesised that PRL signalling leading to mammary epithelial differentiation would contribute to breast cancer suppression," Ali states. Indeed, supported by findings from similar investigations in Japan and the US, the research conducted in Ali's lab has shown, for the first time, that PRL and its intracellular signalling pathway do in fact exert an antitumourigenic influence. By regulating epithelial differentiation in breast cancer cells, PRL's downstream tyrosine kinase, Janus kinase (Jak2), suppresses the signalling activity of the prometastatic pathways that allow for a cancer to spread. A vital aspect of tumour metastasis is the process of epithelial-mesenchymal transformation (EMT) whereby epithelial cells turn into intrusive, migratory mesenchymal cells. Ali found that PRL/Jak2 signalling activates PRL's receptor and reduces the invasive behaviour of breast cancer cells of mesenchymal phenotype. PRL and Jak2's ability to regulate EMT is therefore critical for dampening the spread of cancer once it has developed.

Additionally, interesting results can be found concerning the behaviour of epidermal growth factor (EGF) when confronted with PRL. EGF, a well-known mitogenic factor for mammary epithelial cells, has been shown to inhibit cellular differentiation as mediated by PRL, while PRL has been shown to inhibit cell proliferation as mediated by EGF. Ali's lab has shown that PRL plays a further role yet in stemming the spread of breast carcinogenesis: "We found that when mammary cells are exposed to PRL they become resistant to the effects of growth factors implicated in cancer development," she explains. Mitogen activated protein kinase (MAPK) is involved in a range of important cellular processes but its role in proliferation is cut short through the tyrosine phosphorylation of growth factor receptor-bound protein 2 (Grb2). In this manner, PRL is able to confer resistance on the mammary epithelial cells to EGF's mitogenic effects.

With their discovery of the lactogenic hormone's role in conserving the polarity of mammary epithelial cells and suppressing EMT, Ali's group has been able to adopt a 3D model of cellular morphogenesis for a better understanding of the molecular mechanisms of alveologenesis as regulated by PRL. Although the wealth of knowledge that now exists around this process represents several major scientific advances, PRL's role in regulating mammary morphogenesis and remodelling is known but not understood. With the new morphogenesis 3D cellular model it is hoped that the molecular mechanisms of PRL, and thus breastfeeding, on alveologenesis and breast cancer can begin to be unravelled.

**ALVEOLOGENESIS**

Determining the molecular mechanisms of how lactation might protect women against breast carcinogenesis has led Ali to a dramatic reappraisal of the lactogenic hormone: "We propose that the function of PRL within the mammary gland could serve as a link between breastfeeding and protection against breast cancer". To find this out, Ali has developed two complementary research programmes; one aims to characterise how PRL facilitates alveologenesis and the other to elucidate the role of PRL in the development of breast cancer.

**The groundbreaking studies conducted by Ali’s group in defining a new protective role for the lactation hormone PRL against breast cancer further underscores the importance of breastfeeding in preventing breast tumourigenesis**

Ali has shown that by binding with its receptor, PRL enables the intracellular signalling that leads to the morphological changes of the mammary gland that allow lactation. In doing so, her lab has made new discoveries and reversed previously held assumptions about the molecular mechanisms involved. Downstream of PRL's binding to its receptor (PRLR) it has been found that intracellular proteins, tyrosine phosphatases (PTP), are contributing to the signalling mechanisms. Until then it was thought that PTPs only negatively regulated signalling by dephosphorylation of phosphotyrosine residues, but Ali's investigations prove that PTPs are not so limited. They stabilise the Janus tyrosine kinase (Jak2) and activate the Jak2/Signal Transducer and Activator of Transcription (Stat5) signalling pathway, as it allows cytokines and growth factors to stimulate target genes activation in the nucleus, is vital for normal cell signalling. This, in turn, causes the development of alveolar and differentiation of the mammary gland in a process called alveologenesis so the mammalian breast can synthesise and secrete milk into the mammary ducts.
PATHWAY TO PROGNOSIS

With current funding taking Ali’s present research activities through to 2016, her lab has focused its efforts on cementing the researchers’ discovery that PRL is indeed a suppressant of breast tumourigenesis. Examining clinical cases of human breast cancer, it has been possible to extract further useful information from PRL and its signalling components. Ali has found that as cancer progresses, the PRL pathway is downregulated and can therefore be used as a marker of a good prognosis. Indeed, by studying cases of breast cancer with regards to PRL and the Jak2/Stat5 signalling pathway, it is also possible to identify a better prognosis in patients as less aggressive cancers are flagged by the expression of PRL, its receptor, Jak2, Stat5 and its target milk protein, β-casein. Remarkably, the expression of PRL’s signalling components has been shown to correlate with incidences of relapse-free survival, posing an exciting opportunity for Ali’s group: “We plan within the near future to use PRL clinically for prognosis and treatment against breast cancer,” she reveals.

The major advances in molecular characterisation of breast cancer into five different subtypes (luminal A, luminal B, Human Epidermal grown factor Receptor 2 (HER2), basal-like and, finally, normal breast-like) each with their own distinct clinical outcomes, together with the groundbreaking studies conducted by Ali’s group in defining a new protective role for the lactation hormone PRL against breast cancer, will help in advancing knowledge into the role of breastfeeding in these different breast cancer subtypes. Moreover, with major advances like these in both the fields of PRL and breast cancer research, effective diagnosis and prognosis of cancer patients will be significantly increased as the molecular mechanisms are better characterised in individual cases. Hopefully, these findings and future results will therefore contribute to cancer therapies tailored to the individual. This will be of significant benefit to the future of cancer care, where personalised treatments are being avidly pursued in order to avoid the debilitating toxic complications of chemo- and radiation therapy.

Despite the huge advances toward establishing PRL’s protective effects in reducing the risk of breast cancer, research needs to continue before solid conclusions can be drawn regarding the beneficial role of breastfeeding for mothers. As an issue affecting almost all child-rearing women around the world, Ali believes that a common understanding of its role in the development and progression of cancer needs to be a public health priority. “I am hopeful that our studies will help shed light on the benefits of breastfeeding to women’s health,” she states. The discoveries unearthed in her lab will undoubtedly contribute toward this goal.

INTELLIGENCE

MOLECULAR AND MECHANISTIC INVESTIGATION INTO THE BENEFITS OF BREASTFEEDING IN WOMEN’S HEALTH

OBJECTIVES

To characterise, at the cellular and molecular levels, the role of prolactin (PRL) hormone in the normal functioning of the mammary gland, as well as its role in breast cancer development. As a major lactogenic hormone, these studies should help define the influence of breastfeeding on breast cancer biology.

KEY COLLABORATORS

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