Finding the Molecular Fingerprint of Psychological Resilience in Breast Cancer Patients

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Scientia

FINDING THE MOLECULAR FINGERPRINT OF PSYCHOLOGICAL RESILIENCE IN BREAST CANCER PATIENTS

Professor Carl Borrebaeck and **Dr Ulrika Axelsson** are Director and Deputy Director, respectively, of the CREATE Health Translational Cancer Centre, Lund University, Sweden; a venue with an outstanding record of world-class cancer research. They are leading research into the fascinating topic of whether cancer patients' psychological resilience after their cancer diagnosis may be linked to biomolecular processes, suggesting a mind-body link between the ability to cope psychologically and its impact on cancer prognosis.

Why Do Some People Cope Better Than Others?

Receiving a diagnosis of cancer is a traumatic and life-changing event, and in itself may lead to significant and negative psychological impacts. We know that stress and depression can generally worsen the progression of illness and disease, and patients struggling with psychological problems tend to have a poorer life-expectancy and quality of life. However, it is observable that some patients handle these events with better resilience than others.

Cancer research is increasingly recognising that tumours do not exist in isolation but are part of, and responsive to, the wider body 'ecosystem'. For example, there is growing evidence that the effects of the mind and body are intrinsically joined, so that psychological stresses can have strong detrimental effects on cancer outcomes (prognosis). It remains unclear, however, why some individuals have greater psychological resilience, which is defined as the dynamic process in which individuals adjust, cope and adapt in the face of challenge and adversity.

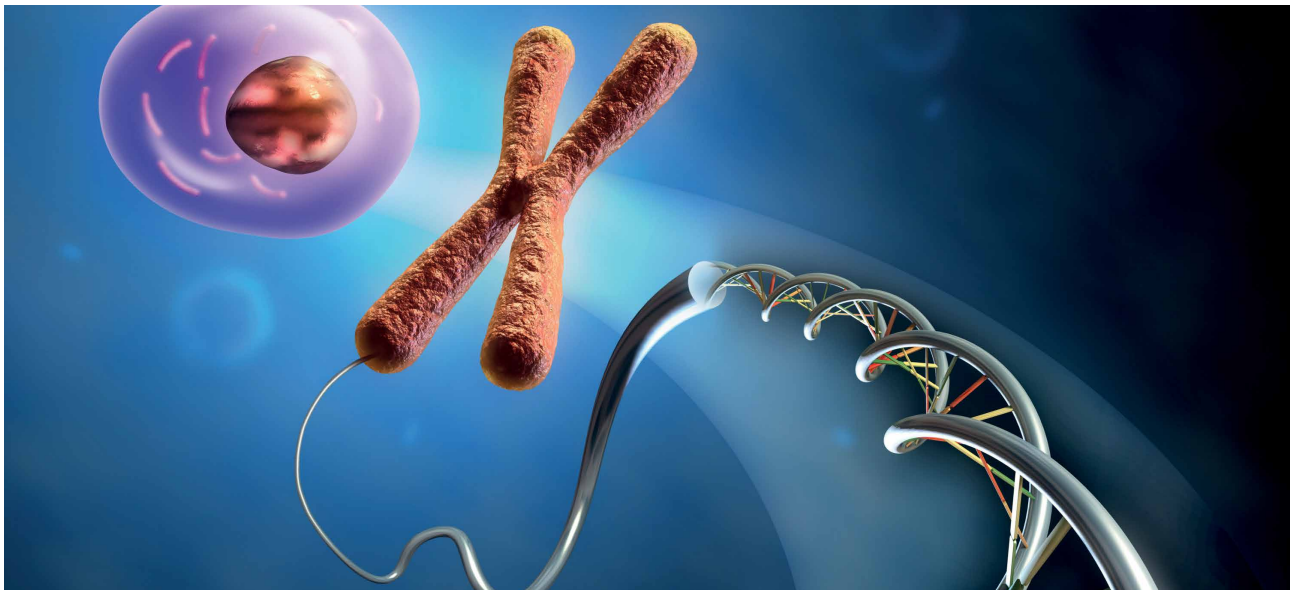
Researchers at the CREATE clinic, Sweden, are hoping to identify biochemical markers that link to and predict low psychological resilience, ideally through a simple blood test. Their long-term goal is to open up new cancer treatments through complementary medical and psychological approaches.

The CREATE project

Professor Carl Borrebaeck and Dr Ulrika Axelsson are Director and Deputy Director, respectively, of the CREATE Health Translational Cancer Centre, Lund University, Sweden. They lead a multidisciplinary research team currently running clinical studies to investigate the relationship between the psychological resilience of cancer patients and biomarker signatures. Working with breast cancer patients,

the CREATE Health project aims to use advanced 'omics' to untangle the intertwined mind-body links between psychological resilience and cancer prognosis.

The vision that resilience had an imprint in the somatic background of humans emerged in the team already 2012 and then grew into the largest clinical study conducted to date with a focus on the body and mind axis, fuelled by advanced omics technologies. Later, a scoping review by Dr Axelsson and her colleagues verified significant gaps in the knowledge regarding the connections between mind and body in the context of cancer. They also noted that there was no established protocol



From DNA to Cell

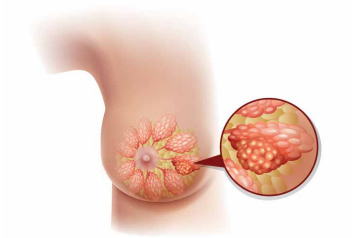


Illustration of Breast Cancer

for how to analyse these potential links, although stress and depression had been shown to affect the likelihood of tumour cells metastasising (the spreading of secondary tumours). Similarly, only a very small number of biomolecular markers had been investigated for their role in psychological resilience.

The present study, denoted as 'SCAN-B Resilience' encompasses over 1,000 patients today and is part of the broader Sweden Cancerome Analysis Network–Breast (SCAN-B) study, which aims to develop new clinical tests for breast cancer. At time of diagnosis, breast cancer patients are asked to complete the Connor-Davidson Resilience scale (CD-RISC), a standardised method to measure psychological resilience, as well as questionnaires to measure their quality of life, lifestyle and socioeconomic status and blood samples were taken for the biomolecular analyses. Patients are followed up at one year with the same questionnaires.

The Search for Biomarkers for Low/ High Psychological Resilience

The CREATE Health project is undertaking the first large-scale study to identify the epigenetic 'fingerprint' of high and low psychological resilience in a group of cancer patients. Epigenetics is the study of changes in living organisms caused by the modification of the way their genes are expressed (as opposed to changes in the genetic code through mutation or damage).

New research fields are rapidly emerging that utilise epigenetic biomarkers as a process to shed light on potential diagnostic methods and therapeutic interventions. In their simplest form, biomarkers are, ideally, easily measurable characteristics that act as an indicator or predictor of a biological process or state. They can be classified into four types: diagnostic biomarkers to determine a specific health disorder; prognostic biomarkers to chart the likely course of a disease; predictive biomarkers to indicate the likely response to a particular drug, and predisposition biomarkers that indicate the risk of developing a disease.

Omics is a catch-all term applied to new technologies that have led to the discovery of many new biomarkers. Omics include a number of investigative research fields including epigenomics, proteomics, transcriptomics and metabolomics that are characterised by high-throughput laboratory techniques that make it possible to gather, in a single experiment, enormous quantities of data about a specific type of molecule, a full set of cellular proteins or a complete set of DNA modifications, for example. While still a relatively new technology, it is moving clinical research in the direction of highly personalised, precision medicine.

Evidence of Mind-Body Interaction

Each person's response to knowing they have cancer and coming to terms with facing the challenges ahead differs hugely. However, it is evident that some people are better than others at psychologically coping, and at the same time have better outcomes, not explained by the type and severity of the cancer or their treatment.

The critical aspects of 'not coping well' or low resilience, can manifest as helplessness, powerlessness and fatalism, which are both symptoms and causes of often debilitating psychological trauma, depression and anxiety. The heterogeneous nature of mental illness, however, makes it difficult for researchers to identify the fundamental physical origins (the

Lund University, Sweden.

aetiology) of the condition(s). Broadly, we know for example, that the brain undergoes pathological changes and a reduction in neuroplasticity, the brain's ability to reorganise itself, often after injury, to create new neural connections. These processes are driven by structural, DNA transcriptional and epigenetic disruptions in several parts of the brain.

An example of the mind-body biomolecular effect is the increase in norepinephrine (a neuroendocrine hormone) during stress. Norepinephrine, in turn, elevates metalloproteinase-9 (MMP-9) levels. Importantly, both depression and stress are related to MMP-9 secretion by tumour-associated macrophages (TAM) in patients with ovarian cancer. TAM cells thus respond to stress and also act to encourage tumour growth by facilitating a proinflammatory tumour environment, creating a two-way, negative cycle of physical and psychological factors.

Professor Borrebaeck and Dr Axelsson are utilising advanced genomics and proteomics research technologies to better understand the biomolecular control of genes related to the level of resilience, in order to identify biomarkers or gene 'signatures' that will reliably signal useful and relevant information.

In this study, blood samples taken from breast cancer patients will be analysed for DNA methylation and micro RNA (miRNA) signatures. DNA methylation is a biological process in which methyl (CH3) groups are added to the DNA molecule, modifying the action of that DNA segment and expression of the genes it contains. miRNA are a class of small non-coding RNAs that control gene expression through a number of different gene translation mechanisms. Emerging research has shown that both miRNA and DNA methylation are likely to play an important role in the manifestation of psychological (and many other) disorders. By analysing patterns and occurrences of DNA methylation and circulating miRNA, omic techniques can identify potential biomarker signatures that may shed light on the complex genetic pathways behind the development of psychological responses and the biomolecular determinants of low or high resilience.

Wider research has identified that DNA methylation is potentially linked to depression through action on several genes, but the findings are preliminary. Similarly, miRNA has emerged as a key regulator of higher brain function and neuroplasticity. Importantly there are also indications that the differential co-expression of a group of miRNAs plays a direct role in human disease pathogenesis, but can also assist researchers to study the nature of the disordered biomolecular pathways involved.

Future Project Aims

At this stage of the CREATE Health research, the team is aiming to validate the value and reliability of using DNA methylation and miRNA as biomarkers for resilience. Uniquely, the project will correlate breast cancer patients' psychological status with the epigenetic results and track their relationship on quality of life and disease burden.

By focussing on the body and mind interactions of these patients, it is hypothesised that biomolecular signatures will match with high or low resilience indicators. Once biomarkers are proven as reliable indicators, simple tests will hopefully be developed that would enable the clinician to identify at an early stage whether a patient with cancer is also particularly susceptible to low-resilience. This information can alert clinicians that the patient faces a greater risk of a poorer cancer outcome and decreased quality of life. Appropriate intervention strategies can then be put in place, which can ameliorate the patient's psychological difficulties.

Establishing a greater understanding of the biomolecular processes behind psychological resilience and the complex progression of tumours and other diseases opens many avenues for future clinical developments. The identification of biomolecular signatures associated with high or low psychological resilience could potentially have a major impact on the patient, as it potentially provides the opportunity for personalised diagnosis and treatment regimens, to address challenging psychological barriers to health improvement.

For clinicians, the tests will identify high-risk patients that were perhaps previously not easily identifiable. This should significantly improve clinical outcomes for cancers by simply addressing the confounding psychological factors to success. However, a detailed understanding of the epigenetics involved will also encourage the development of new, highly targeted medical treatments such as DNA methyltransferase inhibitors, as well as new psychosocial interventions.

Meet the researchers

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Professor Carl Borrebaeck achieved degrees in Chemistry/Maths (BSc) and Chemical engineering (MSci) before achieving his doctorate in Molecular immunology from Lund University (LU), Sweden in 1979. Following postdoctoral studies at the University of California, he returned to LU as an Associate Professor of Immunotechnology in 1981. Professor Borrebaeck received his professorship in 1990 and in 2005 also became Director of CREATE, Health Translational Cancer Centre at LU. Between 2009–2014 he was Vice President of LU. In addition, Professor Borrebaeck is a successful serial entrepreneur, having co-founded multiple biotech companies including Immunovia AB, Senzagen AB, BioInvent International AB, Alligator BioScience AB, and, most recently, PainDrainer AB. Amongst his many awards, Professor Borrebaeck received The Biotech Builders Award for outstanding entrepreneurship in 2017, the Academy of Engineering Science Gold Medal for outstanding research in 2012 and the Akzo Nobel Science Award in 2009.

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Dr Ulrika Axelsson achieved degrees in Chemical engineering (MSci) at the Faculty of Engineering (LTH) at Lund University (LU) before she graduated from LU with a PhD in immunotechnology in 2009 and worked as a Research Scientist in at LU between 2009–2010. Since 2010, Dr Axelsson has simultaneously managed and coordinated a number of key cancer initiatives: first as Research Coordinator, then Deputy Director of CREATE, Health Translational Cancer Centre at LU (2010-date), the LU Cancer centre (Project Leader, 2012–2013), and Research Coordinator at the BioBanking and Molecular Resources Infrastructure of Sweden (2011–2014). Dr Axelsson is also currently the Business Development Manager for PainDrainer AB, Lund, Sweden.

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CREATE, Health Translational Cancer Centre, Lund University

Established in 2005, CREATE Health is a unique strategic centre for Translational Cancer research mainly located at Medicon Village in Lund, Sweden. Offering an equipped and integrated 'omics' hub, CREATE Health brings together multidisciplinary Lund University Hospital researchers and clinicians from the Faculties of Medicine, Natural Science and Engineering to solve complex clinical problems. CREATE Health is primarily focussed on the selection of optimal, individually-based, cancer treatments emerging from the development of novel diagnostics and therapeutics based on identified markers and molecular signatures.

The SCAN-B resilience study and the MAD (Make a difference) for Cancer Programme are both hosted by CREATE. MAD is a unique, collaborative and multi-focused project bringing together holistic research on early diagnosis, patient stratification and targeted therapies addressing all aspects of cancer biology, with the aim of rapid implementation.