Health & Medicine | Courtney W Houchen & Edwin Bannerman-Menson

Targeting cancer stemness
A new approach to target tumour metastasis in colorectal cancer

At COARE Holdings in the US, Dr Courtney W Houchen and Edwin Bannerman-Menson examine innovative ways to target and treat metastatic colorectal cancer (mCRC). Their research focuses on the ‘stemness’ of cancer cells—a property by which the cells within a tumour are able to divide and give rise to every cancerous cell within the tumour. When these cancerous cells leave the tumour and enter the blood stream or lymphatic system, they ultimately invade local and distant tissues. This process is called metastasis. To date, such cancers do not have any cure. COARE and the Houchen lab at the University of Oklahoma Health Sciences Center work together to find molecular markers in these cancer stemlike cells (CSCs) to therapeutically target and arrest mCRC.

Colorectal cancer (CRC) is the third most common type of cancer and the second most common cause of cancer-related death worldwide. 90% of these deaths are due to metastatic colorectal cancer (mCRC). Having a family history of cancers, practising a sedentary lifestyle, eating a diet with unhealthy amounts of processed and low-fibre food, smoking, substance abuse, and a history of inflammatory bowel disease (IBD) all increase the likelihood of a person getting diagnosed with CRC.

Most cancers begin with a group of abnormally divided cells forming a tumour. These abnormal cells undergo further rounds of uncontrolled cell divisions and self-renewals to form more low-density, heterogeneous tumour cells which are resistant to any form of prevalent cytotoxic treatment. These abnormal cells, known as tumour stem cells (TSC) or cancer stemlike cells (CSC), eventually cause the tumour to metastasise with a rapid deterioration in the quality of life of the patient and fatal consequences. Unfortunately, most cases of CRC are diagnosed when they have turned metastatic.

A key reason behind TSC/CSCs escaping the body’s own surveillance mechanism is their similarity to embryonic or tissue stem cells. These cells are involved in regulating some of the key signal-transduction pathways in the body, like the Notch, Hedgehog, and Wnt pathways—all of which are crucial in maintaining homeostasis. These cells have also been shown to lose E-cadherin from epithelial cells—a crucial adhesive molecule which helps the cells to stay localised. This enhances the motility and invasive properties of the TSC/CSCs, cumulatively contributing to cancer stemness.

Despite multiple advances in the field of cancer genomics and therapeutics, nearly 50% of patients face cases of relapse or recurrence at distant sites, wherein the tumour becomes irreparable and eventually becomes fatal. Their involvement in the initiation, growth, and development of diverse forms of cancers make the TSC/CSCs one of the most critical targets for improving clinical outcomes among CRC patients.

COARE’S MISSION: TARGETING THE MARKERS OF METASTASIS
One of the most prominent reasons for cancer metastasis is epigenetic modification—chemical processes within the genome that decide whether the genes will be expressed or not. Some key epigenetic modifications include DNA methylation, histone modifications, and chromatin remodelling. These modifications cause irreversible mutations in tumour suppressor genes and oncoproteins such as APC, KRAS, TP53, and BRAF—all of which have been topics of extensive research in the past.

Dr Courtney W Houchen is professor of medicine at the University of Oklahoma and founder of COARE Holdings. Together with CEO Edwin Bannerman-Menson, he is dedicated to tracing the potential regulatory mechanisms that underlie cancer stemness. COARE have found that DCLK1 as a marker of tumorigenesis and metastasis might be a therapeutic target against metastatic CRC.

One of the most prominent reasons for cancer metastasis is epigenetic modification—chemical processes within the genome that decide whether the genes will be expressed or not. Some key epigenetic modifications include DNA methylation, histone modifications, and chromatin remodelling. These modifications cause irreversible mutations in tumour suppressor genes and oncoproteins such as APC, KRAS, TP53, and BRAF—all of which have been topics of extensive research in the past.

A key reason behind TSC/CSCs escaping the body’s own surveillance mechanism is their similarity to embryonic or tissue stem cells. These cells are involved in regulating some of the key signal-transduction pathways in the body, like the Notch, Hedgehog, and Wnt pathways—all of which are crucial in maintaining homeostasis. These cells have also been shown to lose E-cadherin from epithelial cells—a crucial adhesive molecule which helps the cells to stay localised. This enhances the motility and invasive properties of the TSC/CSCs, cumulatively contributing to cancer stemness.

Despite multiple advances in the field of cancer genomics and therapeutics, nearly 50% of patients face cases of relapse or recurrence at distant sites, wherein the tumour becomes irreparable and eventually becomes fatal. Their involvement in the initiation, growth, and development of diverse forms of cancers make the TSC/CSCs one of the most critical targets for improving clinical outcomes among CRC patients.

One of the most prominent reasons for cancer metastasis is epigenetic modification—chemical processes within the genome that decide whether the genes will be expressed or not. Some key epigenetic modifications include DNA methylation, histone modifications, and chromatin remodelling. These modifications cause irreversible mutations in tumour suppressor genes and oncoproteins such as APC, KRAS, TP53, and BRAF—all of which have been topics of extensive research in the past.

Dr Courtney W Houchen is professor of medicine at the University of Oklahoma and founder of COARE Holdings. Together with CEO Edwin Bannerman-Menson, he is dedicated to tracing the potential regulatory mechanisms that underlie cancer stemness. COARE have found that DCLK1 as a marker of tumorigenesis and metastasis might be a therapeutic target against metastatic CRC.

The group found that DCLK1 was overexpressed in adenocarcinomas in the colon, and the same isoform population also had high numbers of TSCs, hinting at a direct correlation between the two. Moreover, knocking down experiments of the DCLK1 gene resulted in silencing of pro-survival pathways (like Notch, Wnt)/β-catenin, NFκB, and RELA) in these mice also reduced tumourigenesis. These experiments emphasised the role of DCLK1 as a master regulator of multiple pro-survival pathways.

The main focus lay in understanding the basis of DCLK1 involvement in pro-survival pathways and to differentiate the healthy cells from cancerous ones. Since both normal cells and cancer stem cells require similar survival signalling mechanisms, it is difficult for the body to distinguish between the two. The team used the ApoMin+ mouse model, a standard group of mouse models with multiple intestinal tumours, to simulate the human intestinal microenvironment.

Korean researchers led by Park et al.

The team used a mouse model to simulate the human intestinal microenvironment.
Houchen and Bannerman-Menson’s research highlights the therapeutic potential of targeting DCLK1, which has shown its influence on metastasis and tumourigenesis in animal models.

A meta-analysis conducted by Makino et al. (2020) showed that DCLK1 was a master regulator of pluripotency factors such as Nanog, Oct4, Sox2, Klf4, and Myc, which were crucial for cancer cell survival, stemness, and regulation of EMT transcription factors, including Snail, Slug, Twist, and ZEB1. They further highlighted that silencing TRIB3 also led to lowering the EMT cycle. It was also seen that DCLK1 was involved in CRC. Thus, DCLK1 appears to be an attractive target to arrest metastasis in CRC and aligns with COARE’s mission of treating the root cause of metastatic CRCs, among others.

**FUTURE DIRECTIONS**

As well as crocin, there have been a few other therapeutic applications for targeting DCLK1 in studies so far. A promising one is Niclosamide, as demonstrated by Park et al. (2019). This approach disrupted the LEF1–DCLK1 pathway to downregulate the TSC2–CSG and reduce stemness. Honokiol, a biphenolic compound used in traditional Chinese medicine for years, has also been shown to bind to DCLK1 and suppress its activity in vitro (Subramanium et al.).

Houchen and Bannerman-Menson’s research thus highlights the therapeutic potential of targeting DCLK1, which has shown its influence on metastasis and tumourigenesis in animal models. Though larger real-world studies are needed to substantiate this claim, there is no denying that there lies a potential of targeting DCLK1, which has shown its influence on metastasis.