Inflammation and its role in shaping cell responses in cancers

From tumours to T cells, **Dr Cordula Stover** has an impressive research portfolio. Based at the University of Leicester, she originally trained as a medic, before moving into research to address some of the many unanswered questions that she faced on a daily basis. Her work focuses mainly on inflammation, with many previous research projects addressing issues relating to cancer.

The overarching theme of Dr Cordula Stover's research is 'inflammation'. Her ultimate aim is to discern patterns which are applicable to scenarios seen in human disease, but that can be studied using both animal and cell models, and that would be of direct benefit to clinicians. Her work has covered a variety of topics, but she has contributed significantly to the field of cancer, particularly focussing on the role of myeloid derived suppressor cells (MDSCs) in tumour growth, and how they may offer a potential therapeutic target.

MDSCs, INFLAMMATION AND IMMUNE SUPPRESSION

Pro-inflammatory mediators associated with chronic inflammation cause MDSCs, a whole family of cells, to expand and activate. MDSCs are a heterogeneous (diverse) group of cells that originate from the same cells that go on to become blood cells. Normally, MDSCs are responsible for protecting the body from damage caused by overzealous immune responses, but sometimes they also suppress immune responses that are crucial for fighting disease. They cause immunosuppression through several routes, including inhibition of immune cells and preventing the activity of several other cell types.

It is well known that chronic inflammation is linked to an increased risk of cancer, and both inflammation-associated molecules and pro-inflammatory cytokines have been associated with the accumulation and induction of MDSCs. MDSCs are responsible for maintaining the relationship between chronic inflammation and tumour progression; their role in suppressing the body's immune responses is linked to the down-regulation of beneficial anti-tumour responses. Furthermore, MDCSs themselves release pro-inflammatory factors which maintain the inflammatory environment and maintain the MDSC population. MDSCs also contribute to tumour spread, as they directly promote tumour proliferation and metastasis. Due to their lack of surface markers, the most effective way to identify MDSCs is by their immunosuppressive function, or by the accumulation of regulatory T-cells that occurs alongside increased numbers of MDSCs.

This mechanism is just one of many that demonstrates how immune responses

The immune system can both protect the body against tumour growth, and promote tumour spread through suppression of anti-tumour immune responses

generated by the body to try and resolve dangerous situations can actually sometimes do more harm than good. In this case, the immune system can both protect the body against tumour growth, and promote tumour spread through suppression of anti-tumour immune responses.

COMBATING BREAST CANCER

Breast cancer is the most common cancer among women in the UK and results in the second highest cancer mortality rate in women: 11,600 deaths in 2012. Due to the role that MDSCs play in supporting tumour growth and spread, there is potential to target MDSCs to increase survival rates in women with breast cancer.

There are several ways in which MDSCs could potentially be targeted to treat breast cancer. As the cells are immunosuppressive, reducing their activity or accumulation gives the anti-breast cancer immune responses an opportunity to target the tumour. Firstly, MDSCs could be forced to differentiate into more mature states. Secondly, the expansion of MDSCs accumulating at tumour sites could be inhibited through targeting of specific molecules, such as matrix metalloproteinase-9, an enzyme secreted by MDSCs, or tyrosine kinase inhibitors. Finally, the function of the cells could be blocked, possibly using reactive oxygen species to prevent T-cell signalling.

Cellular infiltration of tumours may also help clinicians determine prognosis; high levels of CD8+ T cells (a type of white blood cell) and memory T cells ('experienced' T cells which have previously encountered tumour associated antigens) have been associated with a reduced rate of metastasis or spread of cancer throughout the body.

COMPLEMENT IN ANTI-TUMOUR IMMUNE SURVEILLANCE

When the immune system's first-line defences are breached, a cascade of enzymes is activated in the blood. This has traditionally been called the 'Complement system'. Now we know that Complement shapes cellular activities, particularly of macrophages – white cells which engulf and digest cellular debris, cancer cells or anything else they recognise as being 'foreign' to the body. In the cancer field, Complement is better defined as an enhancer of anti-tumour surveillance and tumour growth, which can also modulate responses to therapeutics and has potential to be involved in combination therapy approaches.

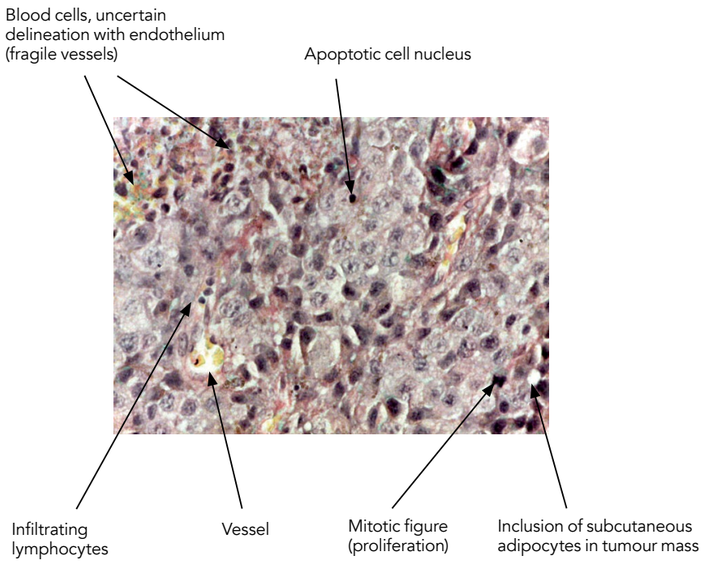
The work of Dr Stover and her group found that patients with progressive pancreatic cancer had higher levels of two molecules, called Complement properdin and Complement receptor 3, than those with stable disease. The implication of this is that Complement properdin is important for enhancing the role of Complement mentioned above. Interestingly, Complement receptor 3 was a component that the group had already earmarked as being important from previous in silico analysis. As work done in the 1950s had suggested a link between Complement properdin and malignant tumours, this finding enabled the group to expand existing knowledge of this innate immune molecule.

Coincidently, reports of a link between a molecule involved in the Complement system and MDSCs led Dr Stover and her team to investigate the impact of Complement properdin, and subsequently to apply methodology on an obese mouse model of tumour growth used to study the increased prevalence of cancer in the obese. This also gave them the opportunity to examine cytokine and chemokine profiles in these mice.

AWAY FROM THE LAB

In addition to her research in a laboratory setting, Dr Stover has contributed to the scientific field in a variety of different ways, not only as Editor of *World Journal of Immunology*, but also as Animal Research Consultant for PLoS One. She takes the view that in some studies, mouse models are vital. For example, it is possible to use gene-targeted mice to infer causality and co-incidence of a phenomenon, and to uniformly alter environment in a population of similar individuals. However, it is important that in vivo work be replaced by cell culture where possible or used to justify findings of ex vivo work. Dr Stover's work has involved an interest in identifying different subsets of macrophages, which led to a project using spleen cells from mice to gauge whether a larger set of in vitro experiments were likely to yield interesting results.

Since joining the field, Dr Stover thinks that she has seen scientific communities looking to find more common ground with other groups, moving away from the idea of working completely in isolation from other, potentially competitive, groups and towards more collaborative projects. She's also observed an increase in inter-disciplinary projects that have the aim of finding mechanisms or observations that can be linked together by a common underlying variable, namely inflammation. Dr Stover sees much scope for increasing the depth of understanding which will impact on the decision making in the treatment of patients either by identifying components in the complexities of disease processes or discovering commonalities that make other modalities adaptable to a particular treatment.



Features of a model tumour resected from mouse (melanoma), and stained with Martius yellow (red blood cells are yellow) and counterstained with Wright's. Tumour cells stimulate proliferation of vessels and shape their own environment.

In addition to her research in a laboratory setting, Dr Stover has contributed to the scientific field in a variety of different ways

Q&A

Could therapeutic strategies for other cancers also target MDSCs?
For a range of solid and haematological cancers, levels of MDSCs have been shown to characterise progression of tumour, its response to therapy or surgery, or survival. In these studies, MDSCs have predominately been used as a biomarker or retrospective stratification tool. It is the presence of MDSCs, however, in the special immune suppressive environment shaped by the cancer that is thought to impede success of other therapies, such as immunotherapy, adoptive transfers or vaccine approaches. The exciting advance in the field is that existing treatments are being re-evaluated for their impact on the expansion and suppressive activities of MDSCs. These drugs could be repositioned to disinhibit innate and adaptive anti-tumour activities and benefit current anti-cancer therapeutic strategies.

If you were awarded £10 million, what project(s) would you like to do?
There would be two areas to invest in: i. to produce sets of guidelines that define for a particular cancer on a common ethical basis the state-of-the-art study model in the advance of knowledge and transferable application; ii. to make more compatible clinical and basic research in a multicentre study by joining from the outset capacities from either set of expertise, thereby pushing the inherent limitations of a singular (clinical or research) approach. I think these two points would significantly address a perceived impediment to real advance.

What has been the biggest achievement of your career so far?
I enjoy the way in which my teaching and research inform one another; I love working up a particular research question like a detective story, to develop new understanding, to guide postgraduate researchers in their scientific pursuit, and, most importantly, to publish. So far, I have 70 publications, and there is still a lot to present.

What has been the biggest challenge of your career so far?
The most difficult by far has been to attract funding for an idea that contravenes a paradigm or does not have immediate impact on patient health, whilst being entirely relevant. As a trend, I can see how discovery is impeded and the kind of cross-disciplinary conversation that is needed to develop stratification of patients or design or repurposing of drugs is not forthcoming.

Have you got any advice for early career researchers, particularly women, who are starting out today?
I don't think there is specific advice for women in particular. I would say that my quest to resist being disheartened in a well justified pursuit, to perfect my analytical skills, to run several projects in parallel and to remain hands-on in the lab has held me in good stead. I think the actual work area in which to develop and apply one's skill sets is less important than the ability to identify a truly career-promoting environment.

Detail

RESEARCH OBJECTIVES

Dr Stover's research focuses on the mechanics of inflammation and how these relate to cancer.

FUNDING

Dr Stover's research received funding from DAAD (German Academic Exhange Service), DFG (German Research Council), MRC, BHF, British Skin Foundation, Asthma UK, Royal Society.

COLLABORATORS

- Dr Michael Browning (University of Leicester)
- Dr Lee Machado (University of Northampton)
- Dr Uday Kishore (Brunel University)
- Dr Andrew Yeudall (Augusta University, Georgia, USA)

BIO

Originally from Germany, Dr Stover gained her Dr. med. (Doctor of Medicine) degree, for experimental work in autoimmune endocrinopathies, from Johannes Gutenberg University, Mainz, Germany and her PhD for experimental work in innate immunity from University of Leicester, Leicester, UK. She is a licensed medical practitioner and is presently Associate Professor (Research and Teaching) at University of Leicester, an Associate Fellow of the Higher Education Academy and STEM Ambassador.

CONTACT

Dr. med. Cordula M Stover, PhD
Assoc Professor
University of Leicester
University Road
Leicester LE1 9HN
UK

E: cms13@leicester.ac.uk
T: +44 (0)116 252 5032
W: https://www2.le.ac.uk/departments/iii/people/dr-cordula-stover
W: https://loop.frontiersin.org/people/41389/overview