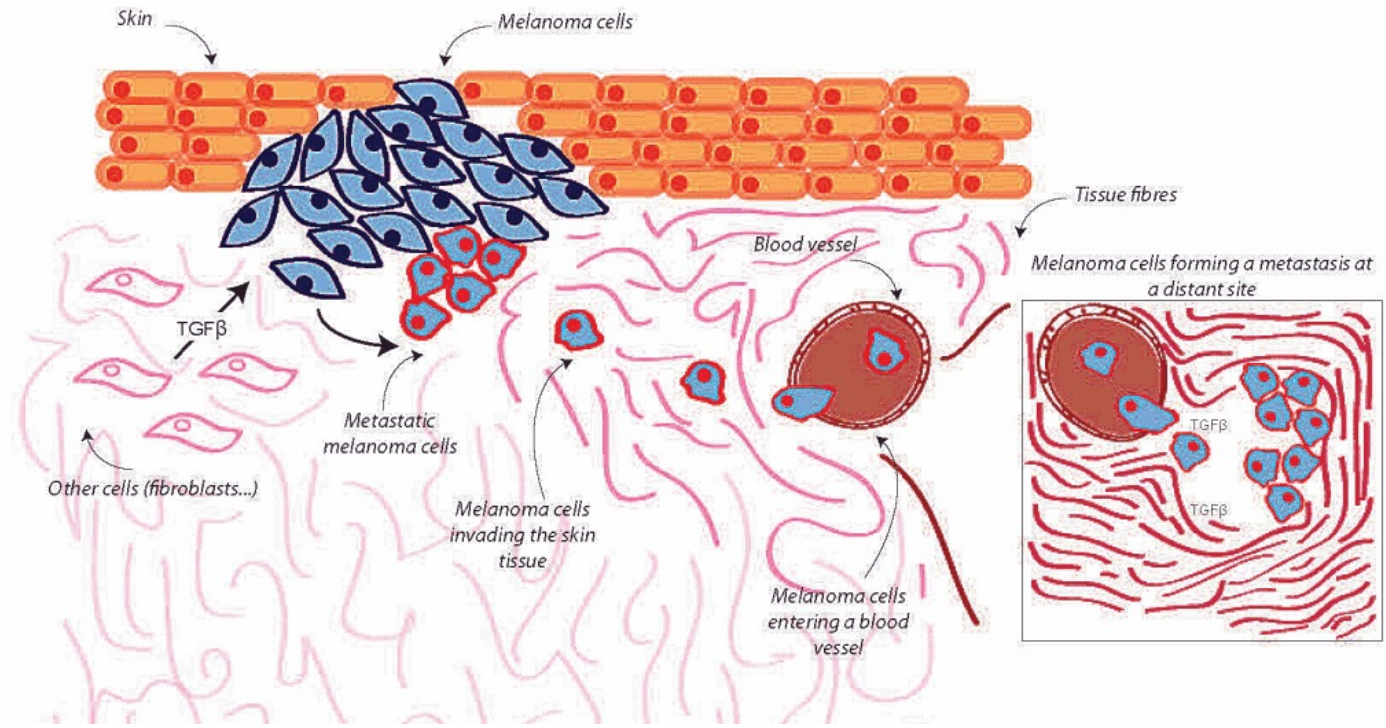
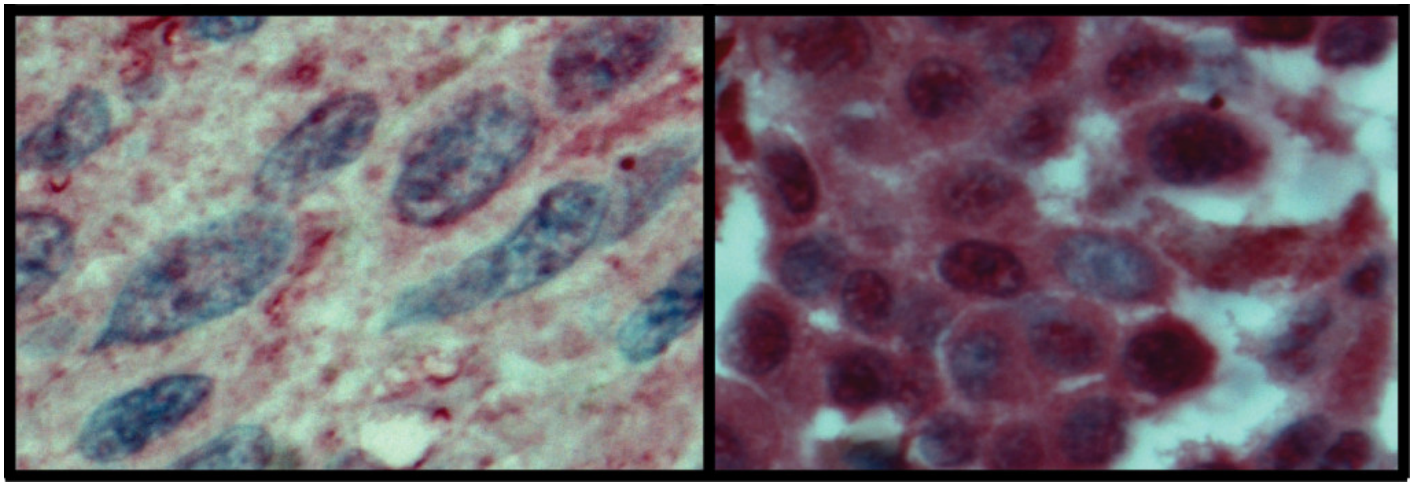
CITED1 is a potential therapeutic target for metastatic melanoma

Cancer kills over 8 million people every year. What makes it so deadly is its ability to spread from the organ where it originates to the rest of the body, a process known as metastasis. Even though science is making huge progress in improving the treatment and survival of patients, we still understand relatively little about how metastasis works. We do, however, know that cancer cells need to acquire several important properties in order to metastasise successfully. For instance, they need to be able to move very quickly, which they normally achieve by contracting and deforming the neighbouring tissue. These are what we call contractile cancer cells. Once cells have invaded the tissue surrounding the original tumour, they usually find a way to enter blood vessels located near the original tumour. They are then transported all over the body by the blood flow, until they find a way to exit the stream and grow again in a completely different part of the body to form a secondary tumour. For example, skin cancer cells can make their way to the lungs or the liver. The aim of this study was to identify molecular pathways that drive the conversion of cancer cells into their highly metastatic form. We chose to work in melanoma - the deadliest form of skin cancer - because it is highly metastatic: nonetheless, all of our findings have the potential to be applicable in other types of cancer.



We have found that a molecule known as TGF? induces the conversion of melanoma cancer cells into their highly metastatic form, that is able to move fast a be contractile. TGF? is produced by both cancer cells and other cell types that are present around the tumour and that are not

malignant. While these cells are not part of the cancer itself, it is possible that their TGF? production might be hijacked by cancer cells to increase metastatic potential. We have subsequently focused on the mechanism through which TGF? changes cancer cells: we have discovered that it does so switching “on” a specific set of genes. Healthy and cancer cells alike are driven by what genes within their DNA are switched “on” and “off”. All cells in the body have the same DNA, which is unique for each individual. However, different cells in different organs switch “on” or “off” different parts of that DNA (which are known as “genes”) to allow them to fulfil specific functions. For example, a muscle cell and a skin cell look and act very differently because different genes within their DNA are switched “on”. TGF? stimulation switches “on” a set of genes within the DNA of cancer cells, which changes their basic blueprint and makes them more contractile and therefore more metastatic. We have found that this process is dependent on a molecule called CITED1, which switches genes “on” after the cell has been activated with TGF?.



Metastatic cancer cells produce more CITED1 than non-metastatic cancer cells.
Samples from melanoma patients of metastatic cells (left) and metastatic cells (right), stained to indicate the levels of CITED1. You can see cancer cells that are highly metastatic have high levels of CITED1.

Interestingly, we have found that melanoma patients that produce a lot of CITED1 have a lower chance of survival than patients who do not. This suggests that the effect of TGF? on cancer cells plays a crucial role in how melanomas metastasise and therefore on the chances of patients to survive. Studies that increase our understanding of the disease are very important for developing new cancer therapies. For example, we think that a drug that stops CITED1 from switching genes “on” would be very effective in stopping melanomas from spreading throughout the body and forming metastases.

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Publication

TGF-?-Induced Transcription Sustains Amoeboid Melanoma Migration and Dissemination.
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