An integrative approach for the exploration of melanoma genetic and immunological interactions

Results in Brief

Melanoma insights could hold benefit for all cancers

The EU-funded MEL-Interactions project demonstrated new tools and experimental models to reveal the genetic, protein and T-cell interactions driving melanomas, advancing personalised cancer treatments.

Malignant melanomas are the main cause of death from skin cancer, with 132 000 deaths annually worldwide. While treatment typically involves surgery, there is a growing interest in the potential of immunotherapies.

Taking melanoma as a model cancer system, the MEL-Interactions project, which was funded by the European Research Council, explored key interactions amongst genes and signalling proteins, as well as between melanoma cells and immune cells, to identify opportunities to improve immunotherapies.

“Our work has already identified promising therapy targets called neoantigens. With several ready for clinical trials, this could benefit around 300 000 melanoma cancer patients per year,” explains Yardena Samuels, the project’s coordinator.
The team’s genomics data, submitted to the open-science database COSMIC, has already allowed other teams to apply techniques such as machine learning in the pursuit of drug targets to treat a range of cancers.

**Melanoma as a model system**

When Samuels set up her lab at the Weizmann Institute of Science 15 years ago, she decided to investigate the little known genetic basis of melanomas. Since then, her team has built a highly annotated tumour bank of over 100 samples. This allowed the team to publish the first melanoma whole exomes, followed by whole genomes.

This databank also provided the foundation for Samuels to investigate the potential of immunotherapies. “Melanomas are one of the most highly mutated solid cancers,” says Samuels. “As mutations are key to immunotherapies, by chance I had chosen a highly relevant cancer type for research into this field.”

**From genes to pathways**

Thanks to information made publicly available through the landmark Cancer Genome Atlas programme, to which Samuels contributed, it is known that melanoma mutant genes divide into four main subgroups: BRAF, RAS, NF1 and triple wild-type.

“There had already been a breakthrough with a small molecule inhibitor for BRAF, mutated in 50% of melanomas, but within six months patients developed resistance,” adds Samuels.

Consequently, Samuels focused on mutation pathways to spot commonalities between subtypes. The majority of tumours harbour a mutation in the same pathway (MAP kinase), which could explain why the mutations are mutually exclusive – pointing to possible drug targets that could treat all subcategories.

“The more we know about these pathways, the more we can target tumours in a highly personalised way,” explains Samuels. Bioinformatics pathway analysis on different mutations helped the team prioritise which to study. The mutant was then cloned and expressed in cells to study outcomes, such as its effect on tumour cell growth and invasion rates.

**Neoantigens as immunotherapy targets**

Samuels’ colleague Steven Rosenberg, had established protocols for a cell therapy that uses tumour-infiltrating lymphocytes (TILs) or white blood cells, to treat solid tumours. While showing promise, it remained unclear what spectrum of
antigens the TILs target.

MEL-Interactions provided important evidence that the TILs target not only tumour-associated antigens but also tumour-associated neoantigens – proteins arising from mutations and harboured by the tumours themselves.

Samuels’ team identified the neoantigens involved and was the first to use immunopeptidomics to identify presented neoantigens that would trigger an immune response. After identifying these responsive T-cells, the receptor specific to this neoantigen could be cloned.

“If we can engineer the T-cells to recognise the neoantigen on the target cell, then immunotherapy will prove more powerful than the current 20-40 % response rate for cutaneous melanoma,” Samuels says.

**Personalised cancer treatment**

The team’s work is applicable to a range of cancers, and neoantigen targets have already been identified for prostate, breast and colorectal cancers, among others.

When building a library of inhibitors or immunotherapy tools for personalised treatment targets, the project has demonstrated the value of investigating low, as well as high, incidence mutations.

But questions remain. “It isn’t clear which mutated proteins drive the cancer process, as opposed to being simple passengers, and not every neoantigen is a good target. We still need to find ways to induce the presentation of neoantigens in cancers with low mutations to create treatment targets,” Samuels notes.

**Keywords**

MEL-Interactions, cancer, melanoma, protein, immunopeptidomics, antigen, neoantigen, immunotherapy, tumour, inhibitor, drugs
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