CANCER

NK cell-regulated tumour dormancy

Nature https://doi.org/10.1038/s41586-021-03614-z (2021)

Disseminated tumour cells (DTCs) are thought to remain in a state of dormancy long after primary tumour resection. The underlying mechanism by which DTCs are induced to become metastatic outgrowth within the distant microenvironments is still incompletely defined. Now, Correia, Bentires-Alj and colleagues identify a role for natural killer (NK) cells in promoting breast cancer dormancy to prevent liver metastasis and further characterise how this effect is counteracted by hepatic stellate cells (HSCs).

Using multiple engineered mouse models that manifested dormant and metastatic readout, the authors first observed that quiescent DTCs were particularly enriched in the liver despite no visible metastatic lesions and showed that adjuvant depletion of NK cells disrupted dormant DTCs and increased hepatic metastatic burden. Transcriptomic analysis and co-culture assays implicated IFNγ signalling as a mediator of NK-cell-imposed DTC dormancy. The authors then shifted the focus to HSCs, which were significantly activated in metastatic stroma and associated with reduced numbers of NK cells. Indeed, activated HSCs were found to secrete CXCL12 and suppress proliferation of co-cultured NK cells, thereby facilitating the awakening of dormant DTC and metastatic outgrowth. Biopsy analysis from patients with breast cancer confirmed a negative correlation between the numbers of accumulated activated HSCs and NK cells.

These findings demonstrate a previously unrecognised mechanism of cellular crosstalk between activated HSCs and NK cells that dictates DTC dormancy during hepatic metastasis in breast cancer. *ZW*

https://doi.org/10.1038/s41556-021-00714-w

STEM CELLS

Lgr6 cells depend on nerves

Cell Stem Cell https://doi.org/10.1016/j.stem.2021.05.007 (2021).

Stem cells rely on close interaction with the niche to maintain their functions. In their latest work, Rompolas and colleagues reveal that Lgr6 epidermal stem cells interact with nerves to regulate their fate and participate in wound healing.

Lgr6 marks a population of basally located stem cells in the interfollicular epidermis. Unlike other stem cell compartments in the hair follicle, its contribution to regeneration was so far unclear. Using intravital imaging in mice, single-cell lineage tracing and cell-ablation methods, the authors confirmed that Lgr6 cells are required for a timely wound healing response. They also uncovered evidence that these stem cells may be regulated by an extrinsic niche.

Upon further probing, the authors discovered that Lgr6 cells physically interact with sensory nerves in the skin. Surgical denervation experiments established that the presence of the nerves was essential for Lgr6-cell-mediated wound re-epithelialization. Interestingly, the loss of this interaction reduced proliferation, altered gene expression and promoted terminal differentiation of Lgr6 populations. The authors concluded that epidermal nerves suppress Lgr6 stem cell differentiation.

In summary, the authors report a unique functional interaction between the Lgr6 stem cell pool and cutaneous nerves that endows them with regenerative features. *CW*

https://doi.org/10.1038/s41556-021-00716-8

PROTEIN QUALITY CONTROL

cGAS senses translation stress

Mol. Cell **81**, 1–15 (2021)

Cyclic GMP-AMP synthase (cGAS) induces innate immunity, including interferon-stimulated genes (ISGs), when sensing foreign or self DNA. Svejstrup and colleagues report that cGAS also detects protein translation stress.

When ribosomes stall, trailing ribosomes may collide into them and halt translation. The ribosome-associated protein quality control factor ASC-1 complex (ASCC) disassembles these stacked ribosomes. Svejstrup and colleagues detected the cGAS-mediated activation of ISGs in ASCC-deficient cells. Using proteomics and a plethora of biochemical approaches, they surprisingly found that this innate immune pathway is activated in these cells due to ribosomes, but not DNA, directly binding to cGAS through the DNA-binding region of cGAS. cGAS redistributed from the nucleus to ribosomes upon different kinds of translation stress. Ribosomes boosted the enzymatic activity of cGAS in a manner that required DNA. It would be of high interest to determine the source of DNA sustaining cytoplasmic stimulation of cGAS at ribosomes.

The report of cGAS activation by stalled ribosomes opens up exciting research avenues. This may be a mechanism used by cells to detect translation stress caused by viruses. Alternatively, compromised protein production may be akin to a damage- or danger-associated molecular pattern that incites inflammatory responses in the absence of infection. *MC*

https://doi.org/10.1038/s41556-021-00719-5

Melina Casadio, Jie Wang, Zhe Wang and Christine Weber

GENOME EDITING

Cas9-based RNA detection

Science **372**, 941–948 (2021)

CRISPR-based RNA detection tools primarily use the RNA-targeting Cas13 system, which detects one target per test. Beisel and colleagues have now reprogrammed the DNA-targeting Cas9 system into a tool that detects multiple RNAs in a single reaction.

In the type II CRISPR system, a trans-activating (tracrRNA) hybridizes to a CRISPR RNA (crRNA), forming a duplex that directs Cas9 to cleave DNA. The authors found that host transcripts outside of the CIRSPR–Cas locus can act as non-canonical crRNAs and pair with the tracrRNA to guide cleavage. Inspired by this unexpected discovery, they designed a Cas9-based RNA detection platform called LEOPARD (leveraging engineered tracrRNAs and on-target DNAs for parallel RNA detection), consisting of a tracrRNA reprogrammed to pair with an RNA of interest, the Cas9 protein, and a fluorescent reporter containing the DNA target. The presence of the given RNA in the sample licenses Cas9 activity, yielding measurable signals. The authors then used gel electrophoresis or a bioanalyzer to detect distinct cleavage products, thereby enabling multiplex RNA detection. As a proof of concept, they applied LEOPARD to detect multiple viral RNAs in a single test and to distinguish SARS-CoV-2 variants in patient samples. Overall, LEOPARD expands CRISPR diagnostic tools by allowing for multiplex RNA detection. *JW*

https://doi.org/10.1038/s41556-021-00718-6