LUNG CANCER

AI to assess images

The distinction between adenocarcinoma and squamous cell carcinoma (SCC), the most prevalent subtypes of non-small-cell lung carcinoma, requires visual examination by a pathologist, and is key to determine the best treatment course for each patient. Aristotelis Tsirigos and colleagues have developed an artificial intelligence (AI)-based strategy to assist evaluation, with results now published.

Publicly available whole-slide images from The Cancer Genome Atlas (TCGA) were used to develop the model: 1,176 from tumour-derived tissue and 459 from non-tumour tissue. The images were split into three groups: training, validation and testing. The researchers developed a model that enables the distinction between non-tumour and tumour tissue with an area under the curve (AUC) of 0.99–0.993, and between adenocarcinoma and SCC with an AUC of 0.949–0.952.

In addition, three pathologists assessed the images: 50% of the images incorrectly classified with the AI-based model were also misclassified by at least one of the pathologists, but 83% of images incorrectly classified by at least one of the pathologists were correctly classified using AI. The classification of the samples was compared with that in TCGA, with AUCs for the algorithm and the pathologists' consensus of 0.82 and 0.78, respectively.

> “there is potentially much more information … to predict the mutational status”

“We also show that there is potentially much more information in these slides to enable the same algorithm to predict the mutational status of frequently-mutated cancer driver genes,” explains Tsirigos. On the basis of previously described associations between gene mutations and specific patterns of lung adenocarcinoma, the system was trained to predict the probability of mutations in the ten most commonly mutated genes in lung adenocarcinoma using matching genomic data available in TCGA. AUC results ranged from 0.640 (0.419–0.845) for *NF1* to 0.856 (0.709–0.964) for *STK11*.

“We anticipate that AI will be useful in clinical practice because it will facilitate the diagnosis process, it will potentially help predict clinical outcomes and it will improve patient selection for clinical trials, particularly for targeted therapies,” summarizes Narges Razavian, adding “However, it is important to emphasize that a doctor should always review any diagnoses and predictions coming from an AI-based system.”

Diana Romero

ORIGINAL ARTICLE Coudray, N. et al. Classification and mutation prediction from non-small cell lung cancer histopathology images using deep learning. *Nat. Med.* https://doi.org/10.1038/s41591-018-0177-5 (2018)

SKIN CANCER

BCC identity switch breaks restraints of Hedgehog pathway inhibition

Credit: Simon Bradbrook/ Springer Nature Limited

Basal cell carcinoma (BCC), a form of skin cancer, is the most common malignancy in humans and typically arises owing to genetic aberrations resulting in constitutive Hedgehog (Hh) signalling. Vismodegib is a drug that inhibits Smoothened, a key component of the Hh pathway, and is approved for the treatment of advanced-stage BCC. Two preclinical studies provide new insights into the responses of BCC to this drug and uncover a clinically relevant strategy to overcome disease relapse.

The majority of patients with BCC benefit from vismodegib, although cures are difficult to achieve and disease relapse can occur after treatment withdrawal. “We showed in mouse models that, indeed, some tumour cells manage to escape the activity of vismodegib and ‘hide’ under a different skin stem cell identity,” states Frederic de Sauvage, who led one of the studies. “By doing so, the residual tumour cells become drug tolerant but are able to switch back to their original identity when treatment is discontinued and the driver pathway is reactivated; tumour growth then resumes.”

Vismodegib-induced tumour regression was mediated by differentiation of BCC cells from a hair follicle stem cell-like phenotype to an interfollicular epidermis or isthmus cell fate. The cells that escaped vismodegib-induced differentiation had activation of Wnt signalling. This switch reflects cellular plasticity via chromatin remodelling, probably in a slow-cycling subpopulation of BCC cells, rather than selection of pre-existing Wnt-expressing cells.

“We demonstrated that combining vismodegib with Wnt pathway inhibitors, which are already being tested in clinical trials, leads to the eradication of resistant tumour cells and avoids tumour relapse in mice,” explains Cédric Blanpain, who led the second study. This finding was broadly consistent across both studies, although the magnitude of the effect seemed to differ, probably owing to variation in the level of Wnt inhibition achieved with an anti-LRP6 antibody in one study versus a Porcupine inhibitor in the other. “The next step would be to conduct clinical trials using such drug combinations in patients with relapsing BCC, and possibly other cancers characterized by activation of the Hh and/or Wnt pathways, such as subtypes of medulloblastoma,” Blanpain opines. “We believe that this mechanism is likely to be at play in other tumour types, such that combinations of existing targeted agents might lead to more complete responses,” adds de Sauvage.

“The two studies have many similarities and, at the same time, nicely complement each other,” says Blanpain. “Even though we use slightly different genetic mouse models, we describe the same mechanism of resistance to vismodegib mediated by a quiescent persistent cell population, which can be overcome through combined Hh and Wnt pathway inhibition. In other words, the same conclusions were reached in both papers, although through different experimental approaches and using different drug combinations, thus reinforcing the validity and relevance of our discoveries,” he concludes.

David Killock

ORIGINAL ARTICLES Biehs, B. et al. A cell identity switch allows residual BCC to survive Hedgehog pathway inhibition. *Nature* **562**, 429–433 (2018) | Sánchez-Danés, A. et al. A slow-cycling LGR5 tumour population mediates basal cell carcinoma relapse after therapy. *Nature* **562**, 434–438 (2018)