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Computational Biology

Major finding: A computational framework termed ExPecto may enable *in silico* prediction of disease risk from DNA sequence.

Concept: ExPecto facilitates tissue-specific prediction of the effects of rare variants on gene expression.

Impact: ExPecto may allow large-scale prediction of disease risk from rare variants to aid precision medicine.

A SEQUENCE-BASED MODEL PREDICTS GENE EXPRESSION FROM GENOMIC VARIANTS

Understanding the effects of genomic alterations is essential for precision medicine. However, the vast range of genomic variations makes it impractical to experimentally determine the effects on disease at the desired scale. Further, currently available predictive models based on matched expression and genotypic data are limited to frequently observed mutations and specific cell or tissue types. To address these challenges, Zhou and colleagues developed ExPecto, a quantitative model that predicts the expression level of genes from sequence information. This approach used a deep convolutional neural network trained to predict 2,002 different histone mark, transcription factor, and DNA accessibility profiles from more than 200 cell and tissue types, facilitating tissue-specific prediction of the epigenomic effects of genomic variants. The ExPecto framework allows prediction of the effects of genomic variation on gene expression from sequence data alone, without training on epigenomic or genomic variant data. The gene expression patterns predicted by ExPecto were highly correlated with transcriptomic data generated by RNA sequencing across tissue types. ExPecto prioritized putative disease-associated variants identified in genome-wide association studies, and the results of 4 top hits in immune-related diseases were experimentally validated. Comparison of ExPecto predictions with data from the Human Gene Mutation Database suggested that ExPecto may be used for large-scale prediction of disease risk. The majority of predicted disease mutations were associated with strong decreases in gene expression, although mutations resulting in overexpression of *TERT* were also identified, consistent with previously reported *TERT* promoter mutations in cancer. These findings demonstrate that ExPecto may facilitate *in silico* prediction of the effects of cancer-associated mutations on gene expression (including rare variants), providing a means to predict the clinical relevance of mutations in a tissue-specific manner at a scale that is not currently feasible experimentally. ■

Zhou J, Theesfeld CL, Yao K, Chen KM, Wong AK, Troyanskaya OG. Deep learning sequence-based ab initio prediction of variant effects on expression and disease risk. Nat Genet 2018;50:1171–9.

Melanoma

Major finding: A neural crest stem cell (NCSC) transcriptional state driven by RXRG underlies relapse in melanoma.

Approach: Single-cell RNA-seq of *BRAF*-mutant melanoma PDXs characterizes minimal residual disease *in vivo*.

Impact: Targeting RXR impairs reprogramming into the NCSC state and delays time to progression.

TARGETING RXR SIGNALING MAY DELAY RELAPSE IN MELANOMA

In patients with melanoma, therapeutic responses are often followed by relapse driven by a small subpopulation of residual or drug-tolerant cells, termed minimal residual disease (MRD). To advance the understanding of the biology of MRD, Rambow, Rogiers, and colleagues performed single-cell DNA and RNA sequencing (RNA-seq) of cells from patient-derived xenografts (PDX) derived from BRAF-mutant melanomas from patients treated with a BRAF/MEK inhibitor combination. MRD contained cells with both low and high expression of the melanoma survival oncogene MITF, expression of which had previously been linked to drug resistance. Single-cell RNA-seq uncovered multiple distinct coexisting drug-tolerant transcriptional states associated with MRD. In one of these states, characterized by high expression of neural crest stem cell (NCSC) markers, the transcriptional program was largely driven by RXRG. The NCSC population was associated with drug resistance. NCSC cells were present in low frequency in drug-naïve melanoma lesions and became more abundant during drug-induced tumor regression, even though cell proliferation is minimal in this phase. Further, the NCSC state was reversible, as drug-induced upregulation of NCSC markers was lost after drug removal, suggesting that MAPK inhibition induces a transient and reversible phenotypic switch to a quiescent NCSC state. Targeting the NCSC population with an RXR antagonist enhanced the antitumor activity of combined BRAF/MEK inhibition. Combined treatment with an RXR antagonist plus BRAF and MEK inhibitors suppressed tumor growth, delaying time-to-disease progression in a melanoma PDX model. The RXR antagonist–mediated reduction in the NCSC state was accompanied by concomitant increases in the other drug-tolerant states, providing further support for the NCSC in driving relapse. In addition to characterizing MRD *in vivo*, these findings suggest that therapeutic targeting of the NCSC state may suppress disease progression and therapy resistance in melanoma. ■

Rambow F, Rogiers A, Marin-Bejar O, Aibar S, Femel J, Dewaele M, et al. Toward minimal residual disease-directed therapy in melanoma. Cell 2018;174:843–55.e19.

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CANCER DISCOVERY

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