BREAST CANCER

Reprogramming ERα

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The transcription factor oestrogen receptor-α (ERα) is expressed in most breast cancers, and the expression of its target genes, which vary between tumours, drives tumour growth and invasion and determines the response to endocrine therapy. Understanding what determines ERα binding to chromatin and what determines target gene selection and expression is therefore important for improving the treatment of patients with breast cancer.

Carroll, Caldas and colleagues mapped ERα chromatin binding using chromatin immunoprecipitation followed by sequencing (ChIP–seq) in frozen samples of primary breast tumours and metastases for which the corresponding clinical history was known. They identified 484 ERα- binding sites that occurred in 75% of the samples. The samples were grouped according to clinical outcome to investigate whether there was a difference in ERα binding between the good prognosis group (which were $ERα^+$ progesterone receptor $(PR)^+$ $HER2^-$) and the poor prognosis group (which were either $ERα^+$ PR^- $HER2^-$ or $ERα^+$ PR^+ $HER2^+$ and which were less likely to respond to endocrine therapy). Differential binding analysis revealed two sets of ERα-bound genomic regions that were associated with either the poor prognosis group or the good prognosis group. The set from the good prognosis group mostly contained oestrogen responsive elements (EREs), whereas the set associated with the poor prognosis group contained EREs and FOXA1-binding motifs; FOXA1 is a pioneer factor that initiates ERα–chromatin binding. Next, the authors generated two gene expression signatures based on the genes that were proximal to the genomic regions associated with either group. Using several independent data sets of gene expression profiles from $ERα^+$ tumours, the good prognosis signature correlated with increased metastasis-free survival, and the poor prognosis signature inversely correlated with metastasis-free survival. Therefore, differential binding of ERα to *cis*-regulatory elements alters gene expression profiles that can be used to predict prognosis.

To determine how ERα binding might be altered, the authors turned to $ERα^+$ breast cancer cell lines. They mapped ERα binding in MCF-7 cells, among others, and the genomic regions that were identified mostly overlapped with those mapped in the poor prognosis group. Because MCF-7 cells were derived from a patient with $ERα^+$ metastatic breast cancer who had not received tamoxifen (an endocrine therapy), the authors proposed that these cells represent an intermediate stage of tumour progression before the acquisition of resistance to endocrine therapy. They found that ERα binding changed in MCF-7 cells that were treated with mitogens that have been shown to induce invasion and resistance to endocrine therapy; these regions were enriched with FOXA1-binding motifs. Indeed, ~53% of the sites that became bound by ERα after mitogen treatment were already bound by FOXA1 or also became bound by FOXA1. Moreover, ERα and FOXA1 were co-expressed in metastases from patients with $ERα^+$ breast tumours.

Together, these data indicate that FOXA1 reprogrammes ERα target gene selection, which advances tumour progression and induces resistance to endocrine therapy. Further investigation is required to understand what regulates FOXA1 binding to *cis*-regulatory elements and how FOXA1 modulates ERα binding; this might simplify the stratification of patients who are at a high risk of developing metastasis and who are likely to have a poor response to endocrine therapy.

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