Nature Reviews Clinical Oncology **12**, 437 (2015); published online 26 May 2015; doi:10.1038/nrclinonc.2015.102

TARGETED THERAPIES

Notching up dormant tumour-cell deaths to avoid recurrence

Most deaths from breast cancer are caused by relapse; minimal residual disease serves as a reservoir of dormant tumour cells that can recur. Assessment of datasets from patients with breast cancer and genetically engineered mouse models of HER2-targeted therapy revealed a crucial role for Notch in tumour dormancy and showed it accelerates tumour recurrence.

Researchers performed a meta-analysis of microarray data in more than 4,400 patients with breast cancer, and showed a strong association between elevated Notch activity and reduced recurrence-free survival, and thus an elevated risk of tumour recurrence. In primary tumour cells derived from a mouse model of breast cancer, HER2 downregulation resulted in Notch activation. Conversely, intact HER2 signalling blocked Notch activation via bypass signalling pathways. In colony-formation assays, Notch activation rescued colony formation in the absence of HER2 signalling, and Notch signalling was sufficient to promote mammary tumour recurrence following HER2 downregulation. Importantly, Notch inhibition resulted in the depletion of dormant residual tumour cells. Consistent with this, treatment of HER2-dependent tumours with inhibitors of Notch resulted in dose-dependent inhibition of tumour recurrence.

Thus, Notch inhibition by genetic or pharmacological approaches prevented tumour recurrence in mice; these data indicate that, in the adjuvant setting, drugs targeting the Notch pathway might eliminate dormant residual cells and prevent tumour recurrence.

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Original article Abravanel, D. L. *et al*. Notch promotes recurrence of dormant tumor cells following HER2/neu-targeted therapy. *J. Clin. Invest*. doi:10.1172/JCI74883