Most probably, the relatively low affinity of tail phosphorylation sites is compensated for by the effectively high local concentration of these sites around the kinase catalytic site in the active EGFR dimer. The suboptimal design of the tail sites is predicted to be essential for quick dissociation from the kinase active site upon phosphorylation, thus preventing substrate-mediated inhibition. The optimal primed tandem YY motif (YpY) within Shc1 facilitates efficient phosphorylation by EGFR in the absence of additional docking interactions and probably also dissociates quickly from EGFR after phosphorylation, thereby avoiding substrate-mediated inhibition. In contrast, Mig6—which has anchor points such as segment 1 (ref. 13) and a hypothesized segment 0 (ref. 14) in addition to the tandem YY motif—remains bound to EGFR after phosphorylation of the YpY sequence. In the case of Mig6, the priming pocket on EGFR traps the product of the phosphorylation reaction (pYpY) and essentially becomes another anchor point for binding of the inhibitor. These distinct modes of binding underscore a complex spectrum of mechanisms of substrate recognition by the EGFR kinase (**Fig. 2**).

The studies also expand knowledge of the role of the Src kinase in regulation of EGFR signaling. Src has been demonstrated not only to potentiate EGFR-dependent DNA synthesis but also to operate synergistically with EGFR in increasing migration and anchorage-independent growth[15,16]. Although the mechanism for this cooperativity between Src and EGFR is largely unclear, it has been proposed to involve Src-mediated phosphorylation of the activation loop of EGFR, hence resulting in recruitment of the downstream substrate STAT5b[17]. The current studies have established the crucial contribution of Src to EGFR signaling by priming substrates for enhanced phosphorylation by EGFR. Src is thus able to influence EGFR signaling both positively, through activation of the Shc-MAPK pathway, and negatively through inhibition driven by Mig6. The ability of Src to tune the net effect of EGFR activation probably explains the pleiotropic effects of Src on the regulation of EGFR signaling and provides a new platform for understanding how Src and EGFR cooperate in mediating resistance to EGFR-targeted therapies in cancer cells[18].

Like EGFR, most kinases may conceivably use multiple mechanisms to recognize and phosphorylate their substrates in a specific fashion. The resulting complexity represents a major challenge in identifying new substrates of kinases and understanding the mechanism of their recognition. Recent bioinformatics approaches have enabled exciting attempts to understand kinase-substrate interactions on the scale of the entire kinome, through systematic identification of the key kinase-domain residues that are important for determining substrate specificity[19]. Further work like the elegant studies by Eck, Cho and colleagues[3] and Cantley and colleagues[4] discussed here will be vital to expand understanding of the individuality of substrate recognition for each kinase.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

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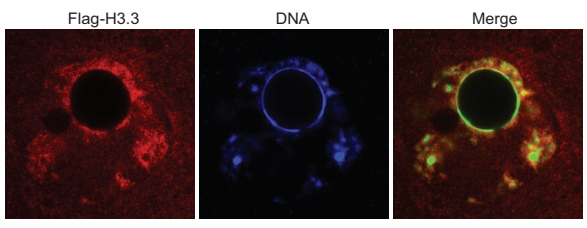
Replication- and transcription-independent histone exchange in oocytes

Turnover and exchange of histones and their variants has long been believed to be negligible in postreplicative cells. This view has been challenged by recent studies in postmitotic neurons (for example, *Neuron* **87**, 77–94, 2015), in which histone-variant exchange was observed during neuronal activity–dependent gene expression. Now, Hajkova and colleagues show that histone-variant exchange also occurs during mouse oogenesis, even in the absence of transcription (*Mol. Cell*. doi:10.1016/j.molcel.2015.10.010, 5 November 2015).



Postnatal mammalian oocytes undergo several developmental transitions in the absence of DNA replication, thus making oogenesis an ideal system to study replication-independent histone dynamics. Using this system, the authors found that microinjection of mRNA for Flag-tagged histone H3.3, but not Flag-tagged canonical histones H3.1 and H3.2, led to incorporation of the histone into the chromatin of growing oocytes. Unexpectedly, new H3.3 incorporation was also seen in transcriptionally inert germinal vesicle–stage oocytes (pictured). Oocyte-specific deletion of Hira, a histone chaperone required for H3.3 incorporation, abolished incorporation of microinjected H3.3 and led to chromatin decondensation accompanied by signs of DNA damage. Single-cell RNA and bisulfite sequencing showed that Hira is necessary for normal gene expression and *de novo* DNA methylation during oocyte development.

This study provides further evidence that histone replacement in postmitotic cells is physiologically important. Such exchange could be important for cell type–specific transcription and plasticity in response to external cues as well as for maintaining genome integrity. It will be interesting to determine whether H3.3 exchange also occurs in other nonproliferating cells.

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