Title: A fine balancing act: a delicate kinase-phosphatase equilibrium that protects against chromosomal instability and cancer

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A fine balancing act: a delicate kinase-phosphatase equilibrium that protects against chromosomal instability and cancer.

Running title: Balancing kinases and phosphatases at the kinetochore.

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Cancer cells rewire signalling networks to acquire specific hallmarks needed for their proliferation, survival, and dissemination throughout the body. Although this is often associated with the constitutive activation or inactivation of protein phosphorylation networks, there are other contexts when the dysregulation must be much milder. For example, chromosomal instability is a widespread cancer hallmark that relies on subtle defects in chromosome replication and/or division, such that these processes remain functional, but nevertheless error-prone. In this article, we will discuss how perturbations to the delicate kinase-phosphatase balance could lie at the heart of this type of dysregulation. In particular, we will explain how the two principle mechanisms that safeguard the chromosome segregation process rely on an equilibrium between at least two kinases and two phosphatases to function correctly. This balance is set during mitosis by a central complex that has also been implicated in chromosomal instability - the BUB1/BUBR1/BUB3 complex – and we will put forward a hypothesis that could link these two findings. This could be relevant for cancer treatment because most tumours have evolved by pushing the boundaries of chromosomal instability to the limit. If this involves subtle changes to the kinase-phosphatase equilibrium, then it may be possible to exacerbate these defects and tip tumour cells over the edge, whilst still maintaining the viability of healthy cells.

Introduction

Protein phosphorylation is critical for regulating protein function, propagating intracellular signals, and maintaining cell and tissue homeostasis (Day et al., 2016). It is not surprising, therefore, that dysregulated phosphorylation is a major cause of several human diseases, including cancer (Creixell et al., 2015; Fleuren et al., 2016). In the context of cancer, mutations within key oncogenes or tumour suppressors enable tumour cells to acquire characteristic traits needed for their growth, survival, and metastasis (Hanahan and Weinberg, 2011). These mutations are frequently associated with the constitutive activation, inactivation, or rewiring, of protein phosphorylation networks (Creixell et al., 2015; Fleuren et al., 2016; Julien et al., 2011; Reimand et al., 2013). For example, the ability to sustain uncontrolled proliferation can result from the hyperactivation of tyrosine kinase receptors, such as EGFR (Henson et al., 2017), the inactivation of other receptor types, such as TGF-beta (Huang and Blobe, 2016), or the constitutive activation of downstream signalling intermediates, such as Ras (Stephen et al., 2014), Raf (Holderfield et al., 2014) or PI3-Kinase (Lim et al., 2015). In addition, this can be supported by the inactivation of tumour suppressor phosphatases, such as PTEN (Lim et al., 2015) or PP2A (Grech et al., 2016), or the activation of oncogenic phosphatases, including many members of the Protein Tyrosine Phosphatase (PTP) superfamily (Hardy et al., 2012; Julien et al., 2011). In this way, tumour cells are able to grossly alter their 'phosphatome' in a manner that best befits their continued proliferation and survival.