the light of this acting to induce stress. They found that acentrosomal cells did not arrest in G1 phase unless an additive secondary stress was also present. Moreover, flies without centrosomes can develop into adults with normal timing and without a G1 phase arrest, showing that within the context of a developing organism the centrosome is completely dispensable for cell cycle progression (Basto et al., 2006). Thus, it is not the absence of a centrosome per se that triggers an arrest in G1 phase. More likely, the p38 kinase-p53-dependent stress response is triggered in cells that contain abnormal centrosomes.

**REFERENCES**


activates Polo-like kinase-1 (Plk1), MAPK, and the Greatwall kinase, all of which also phosphorylate and activate Cdc25C. Finally, it inhibits the activity of the inhibitory kinases Wee1 and Myt1 either directly or via the Greatwall kinase (Jackson, 2006). The alignment of the microtubule-bound chromosomes at the metaphase plate triggers the passage through the spindle checkpoint between metaphase and anaphase. Mechanistically, this is due to the activation of the anaphase promoting complex/cyclosome (APC/C), which triggers the polyubiquitination and proteasomal degradation of cyclin B1 and the inactivation of Cdk1 (Figure 1).

Figure 1. Regulation of the Activity of Cdk1 during the Transition from G2 to M and during Mitosis: the Role of Lzts1
Lzts1 binds Cdc25C and stabilizes it during mitosis (see box). Cdc25C levels drop when Lzts1 is partially or totally lost. The resulting low activity of Cdk1 promotes the premature transition from metaphase to anaphase and gives rise to aneuploidy (see text for details).

An article by Vecchione et al. in a recent issue of Cancer Cell identifies yet another player that contributes to the fine-tuning of the molecular events that determine progression through mitosis and define the spindle checkpoint (Vecchione et al., 2007). The new player is a 596 amino acid protein that is encoded by the tumor suppressor gene Lzts1, that maps to human chromosome 8p22. Chromosomal deletions encompassing Lzts1 are frequently observed in a variety of human cancers including breast, lung, gastric, esophageal, prostate, and bladder cancer. The product of the Lzts1 gene is the founding member of a three member family of proteins, all of which harbor leucine zipper Fez domains (Cabeza-Arvelaiz et al., 2001; Teufel et al., 2005). Earlier studies had clearly shown that reconstituting the expression of Lzts1 in 8p22 deleted tumor cells induces a G2/M arrest. However, the detailed and elegant experiments reported in this new study are the first to address the physiological role of this protein in cell cycle regulation. In addition, they are the first to address the molecular mechanism by which its downregulation promotes oncogenesis. These experiments have shown that Lzts1 binds Cdc25C during mitosis and protects it from proteasomal degradation. As a result, Lzts1 specifically regulates the transition through and not the entry into mitosis, which is not surprising, given the fact that entry into mitosis depends primarily on the activation of Cdc25B and Cdc25A (Lindqvist et al., 2005).

Mutations that affect the regulation of the cell cycle are very frequent in cancer. The first tumor suppressor gene to be identified (Rb) and the most frequently mutated gene in human cancer (p53) play major direct roles in cell cycle regulation. Many of these genes affect the G1 phase of the cell cycle. Mutations targeting cell cycle regulators that function in the G2 and M phases of the cell cycle are apparently less frequent, perhaps because major perturbations affecting these phases are lethal. Nonlethal mutations that alter the fine-tuning of the molecules that control the passage through G2 and M, however, do occur. One such mutation is the deletion of Lzts1. Vecchione et al. show that downregulation or loss of Lzts1, interferes with the activation of Cdk1 during mitosis. The relatively low activity of Cdk1 during the passage through prophase, prometaphase, and metaphase interferes with the regulation of
Actin on Multiple Fronts to Generate a Muscle Fiber

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DOI 10.1016/j.devcel.2007.03.011

How the actin cytoskeleton is harnessed to fulfill its diverse cellular functions is a recurrent and intriguing question. In this issue of Developmental Cell, Kim et al. and Massarwa et al. describe a new role for F-actin, and more specifically the actin regulator WASp, in myoblast fusion in Drosophila.

There are instances during development where a cell relinquishes its individual status to fuse with another, thereby creating a new, multinucleated entity. Development of vertebrate skeletal muscles through the fusion of differentiated myoblasts is one example. In Drosophila, a similar process of fusion takes place to form the embryonic body wall muscles, each of which comprises a single syncytial muscle fiber. Much of what we know about myoblast fusion in vivo comes from studies that have taken advantage of this genetically amenable system. These fibers are the products of fusion between two types of myoblasts: the founder myoblasts, which are endowed with information pertaining to muscle identity and seed the development of each muscle, and the fusion-competent myoblasts (fcm), which contribute to muscle mass through fusion with the founders (Figure 1; Dworak and Sink, 2002).

Shortly after they are born, founders migrate to locations just beneath the epidermis, leaving the fcm within the deeper recesses of the mesoderm. Through the expression of adhesion receptors Dumbfounded (Duf; also known as Kin-of-Irre [Kirre]) and Roughest (Rst; also known as Irregular

the spindle checkpoint and facilitates the premature transition of dividing cells from metaphase into anaphase. The result is chromosomal instability (CIN) and aneuploidy. Heterozygous ablation of Lzts1 is sufficient to downregulate Lzts1 expression and to interfere with the regulation of Cdk1 during progression through the early phases of mitosis. As a result, loss of heterozygosity (LOH) in the Lzts1 locus is not required for tumor induction. The data in the Vecchione et al. study raise new important questions of which the most urgent is the expression of Lzts1 and the regulation of its binding to Cdc25C as the cells progress through the cell cycle. Changes in these parameters, combined with an understanding of the factors that trigger them will allow us to fully integrate Lzts1 into the networks that contribute to the physiological regulation of the cell cycle.

The logical consequences of the data in this paper include the following: (1) Other molecules that, like Lzts1, positively regulate the activity of Cdk1 and whose inactivation is not lethal, are likely to function as tumor suppressors. Previous studies have indeed shown that cells that are depleted of RASSF1A, a protein which inhibits premature degradation of cyclin B1, exhibit increased sensitivity to transformation (Song et al., 2004). (2) Partial inhibition of Cdk1 by small molecules that target Cdk1 or its regulators may have undesirable side effects because they may enhance CIN and promote aneuploidy. (3) Aneuploidy may be caused by mechanisms other than the partial inhibition of Cdk1, such as regulatory and structural defects in centrosome duplication and spindle assembly. In yeast for example, 100 different mutations giving rise to CIN have been identified to date (Rajagopalan and Lengauer, 2004). Diverse mutations leading to CIN and aneuploidy may synergize with mutations that downregulate the activity of Cdk1 because cells in which Cdk1 activity is downregulated may bypass checkpoint activation by these aneuploidy-inducing mechanisms.