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Cell Cycle News & Views

Short-circuiting the cell cycle for cancer therapy

Comment on: Carrassa L, et al. Cell Cycle 2012; 11:2507–17; PMID:22713237; http://dx.doi.org/10.4161/cc.20899

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DNA damage and genomic instability are central both to the evolution and treatment of cancer. As a result, in recent years, much interest has focused on cellular DNA damage responses and whether these can be manipulated for therapy.[1] DNA damage activates a complex, interacting web of DNA repair and cell cycle checkpoint processes that offer a diverse range of potentially druggable targets.[1] These include multiple protein kinases that signal the presence of damage, such as ATM, ATR, Chk1 and Chk2, but also enzymes involved in DNA repair per se such as PARP-1 and MGMT.[2]

Chk1 in particular has attracted attention as a target for drug development, largely because it is a key effector of multiple cell cycle checkpoint responses triggered by both DNA damage and replication arrest.[2] Preclinical evaluation of Chk1 inhibitors has generally concentrated on determining whether checkpoint override can potentiate tumor cell killing by conventional genotoxic agents. Many published studies support this concept, and some, although not all, found greater potentiation in cells lacking p53 function, suggesting a mechanism of tumor selectivity. More recently, however, interest in the therapeutic potential of Chk1 inhibitors as single agents has been growing. Some tumor cells at least appear to be crucially dependent on Chk1 for proliferation and survival, perhaps because oncogene activation creates endogenous DNA damage or replication stress.[3,4]

In a recent paper in *Cell Cycle*,[5] Carrassa and colleagues noted that a panel of tumor cell lines varied greatly in their inherent sensitivity to a Chk1 inhibitor, PF00477736. Postulating that this might reflect variable expression of unknown factors exhibiting "synthetic lethal" interactions with Chk1, they undertook an siRNA screen for protein kinases whose depletion synergized with Chk1 inhibition.[5] Remarkably, the top hit in this screen was Wee1, a dual-specificity protein kinase that catalyzes inhibitory phosphorylation of Cdk1 (primarily on tyrosine 15; Y15). This modification increases as cells progress though the cell cycle, restraining Cdk1 catalytic activity until the onset of mitosis, when Y15 phosphorylation is abruptly reversed through the action of Cdc25 phosphatases (**Fig. 1**).

Carrassa et al. demonstrate that whereas siRNA depletion of Chk1 or Wee1 individually is relatively innocuous, simultaneous depletion of both led to high levels of spontaneous cell death in a wide range of tumor lines.[5]

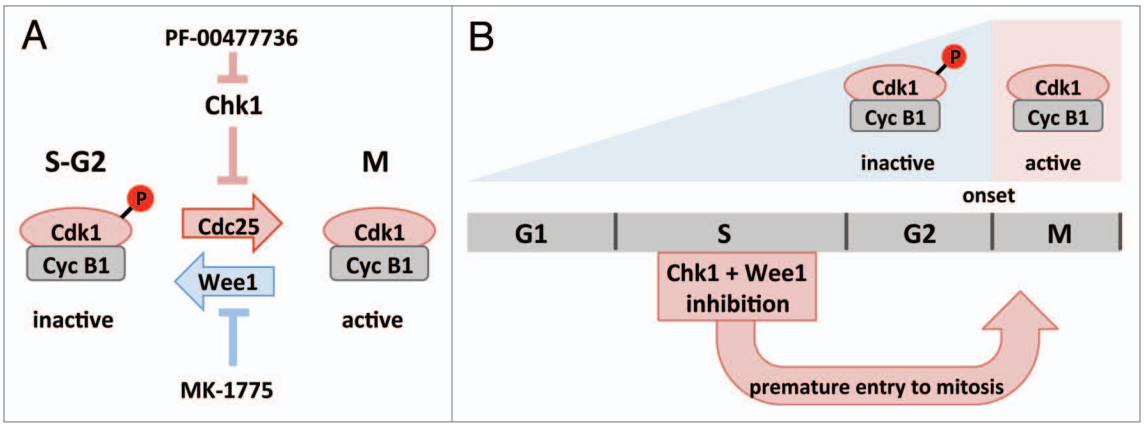

Figure 1. Regulation of Cdk1 inhibitory phosphorylation during normal cell cycle progression (A) In S- and G_2-phases the catalytic activity of Cdk1:cyclin B1 complexes is restrained by inhibitory phosphorylation of tyrosine 15 (Y15), a modification catalyzed primarily by the Wee1 kinase. Cdk1 is also subject to inhibitory phosphorylation on threonine 14; however, this is omitted here for clarity. Entry to mitosis is triggered by rapid removal of Cdk1 Y15 when the activity of Cdc25 phosphatases outstrips that of Wee1 as a result of multiple positive feedback loops.[8] In response to DNA damage, Chk1 is activated and triggers G_2 checkpoint arrest by inhibiting Cdc25 activity and thus maintaining Cdk1 in its Y15 phosphorylated, inactive state while damage persists. PF-00477736 is a Chk1 inhibitor that can override DNA damage-induced G_2 arrest by preventing inhibition of Cdc25 phosphatases by Chk1. MK-1775 is a potent and selective inhibitor of Wee1 kinase. (B) During normal cell cycle progression, Y15 phosphorylated, inactive Cdk1:cyclin B complexes accumulate during S-phase and G_2. Only at the end of G_2 does Cdc25 phosphatase activity rise rapidly to abruptly dephosphorylate and activate Cdk1 and thus trigger the onset of mitosis.[8] Carrassa et al. demonstrate that concurrent inhibition of Chk1 and Wee1 using a combination of PF-00477736 and MK-1775 causes a wide range of tumor cell lines to arrest in S-phase and then to enter mitosis prematurely with partially replicated DNA, leading to mitotic catastrophe and cell death. The S-phase arrest could be due to high levels of replication fork stalling and collapse, which have been shown to occur when Chk1 is inhibited or, alternatively, because premature entry to mitosis extinguishes DNA replication. The unscheduled dephosphorylation and activation of Cdk1 that leads to premature entry to mitosis most likely results from unrestrained Cdc25 phosphatase activity combined with inhibition of the normal tonic level of Wee1 Y15 kinase activity present in S-phase.

Importantly, synergistic cell killing was also obtained using PF00477736 in combination with a small-molecule inhibitor of Wee1, MK-1775, indicating that this synthetic lethal effect can be reproduced pharmacologically. Interestingly, toxicity did not correlate with the p53 status of the tumor cell lines, nor was synergy observed in non-transformed MRC-5 cells, suggesting that synthetic lethality depends on some generic but as-yet-unknown feature of the tumor cell phenotype.[5]

Prolonged maintenance of Cdk1 Y15 phosphorylation via Chk1-mediated inhibition of Cdc25 phosphatases forms an important component of the G_2 arrest mechanism that prevents cells with damaged DNA entering mitosis (**Fig. 1**), but what is the basis for synergistic cell killing by combined inhibition of Chk1 and Wee1 in the absence of exogenous genotoxic stress? Carrassa et al. observed that cells treated with a combination of Chk1 and Wee1 inhibitors arrested in S-phase of the cell cycle but, strangely, were no longer active in DNA synthesis.[5] Tellingly, levels of Cdk1 inhibitory phosphorylation were severely diminished, and consistent with this, morphological analysis revealed that many of these S-phase cells had entered a premature mitosis characterized by partially replicated, pulverized chromosomes and malformed mitotic spindles.[5] Some of these cells subsequently proceeded to die by apoptosis; however, it seems unlikely that such a catastrophic short-circuit from S-phase to mitosis would be survivable in any case (**Fig. 1**).

This and other recent studies[6,7] reveal a more extensive role for Wee1 in cell cycle regulation than was previously known and highlight its potential as an anticancer drug target. But can this synthetic lethal principle of short-circuiting the cell cycle through combined inhibition of Chk1 and Wee1 really be extended to the clinic? Only time will tell, but it is promising that the combination of Chk1 and Wee1 inhibitors potently inhibited the growth of tumor xenografts in vivo with little toxicity as well as killing cells in vitro. As always, more research is needed!

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Vacuolar dynamics and replicative aging

Comment on: Gebre S, et al. Cell Cycle 2012; 11:2176–88; PMID:22622083; http://dx.doi.org/10.4161/cc.20691

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Often described as the counterpart of the mammalian lysosome, the yeast vacuole is the destination for cellular constituents targeted for degradation by autophagic processes. However, the vacuole serves other roles, for instance, as a regulator of cellular ion homeostasis and a storage reservoir for nutrients, metal ions and other metabolites.[1]

The vacuole is also dynamically regulated, both in number and size in response to environmental conditions, including those linked to replicative lifespan.[1] For instance, nutrient restriction, which extends lifespan or the number of daughters that one mother can produce, causes yeast cells to undergo vacuolar fusion events, leading to one large vacuole in place of the 4–5 that normally exist under nutrient-replete conditions. In contrast, osmotic stress leads to enhanced fission and the production of several small vacuolar fragments. In a recent report, Gebre et al. examine the relationship between vacuolar fusion and longevity, finding that overexpression of Osh6, an oxysterol-binding protein that mediates membrane sterol deposition, enhances longevity.[2]

Several yeast genes are required for vacuolar fusion, and in their absence, yeast vacuoles appear as a multitude of vesicles. Among these are *ERG6*, which is required for ergosterol synthesis,[3] and *NYV1*, which encodes a vacuolar SNARE complex component.[4] Both of these genes are also required for lifespan extension by calorie restriction.[5] Also required are the set of OSH genes; in the absence of all seven, vacuoles are fragmented.[6] Gebre et al. tested whether overexpression of any OSH gene rescued defects of other fragmentation mutants, finding that elevated Osh6 levels restored fusion in a *nyv1*Δ background.[2] Overexpression of Osh6 did not rescue the *erg6*Δ, presumably because these genes act in the same pathway involving sterol synthesis and vacuolar membrane deposition. They then showed that OSH6 overexpression led to extension of replicative lifespan. These findings point to Osh6 as having a specific role in modulating vacuolar membrane sterol content and a potential relationship between this function and longevity.

Another piece of evidence that vacuolar fusion may be important for longevity in yeast comes from the observation that vacuolar membranes become disordered in replicatively old cells.[2,5] Thus, enhanced fusion driven by Osh6 overexpression may help maintain vacuoles in a normal state later in the lifespan of a yeast cell. It remains unclear, however, why this matters, particularly since young yeast cells can proliferate normally with fragmented vacuoles. One possibility comes back to the starvation response, in which autophagy becomes important for survival, as fusion events promote mixing of autophagic cargoes with vacuolar enzymes. Genome-wide transcriptional studies suggest that old cells attempt to initiate a starvation response. If vacuolar fusion is important for autophagic flux under these conditions, then defects in this process may compromise continued yeast viability and proliferation. A related view would be that vacuolar fragmentation may be an

indicator of altered lipid composition in vacuolar membranes resulting from age-related elevation of autophagosome-fusion events.[5]

Reduced TOR signaling enhances lifespan in a wide range of organisms including yeast.[7] Recent studies show that the TORC1 complex localizes to the vacuolar membrane and mediates vacuole fragmentation.[8,9] Gebre et al. speculate that elevated Osh6 levels may inhibit TORC1 function at the vacuolar membrane, tipping the balance toward fusion.[2] Consistently, Osh6 overexpression failed to further enhance the long lifespan of a *tor1*Δ strain, suggesting that the two genetic interventions may be leading to lifespan extension through similar mechanisms. One final possibility that cannot be ruled out is that Osh6 overexpression may affect lifespan in part through vacuole-independent mechanisms, since Gebre found unexpectedly that expression of sterol synthesis genes was reduced under these conditions. Of course, many of these possible pathways are non-exclusive, and Osh6 overexpression may affect replicative aging through multiple mechanisms.

Many yeast aging genes have been identified, and it is paramount that the field begins to understand why altered expression of these genes affects longevity. The study by Gebre et al. points to a role for the vacuole in longevity control and possibly link this organelle to calorie restriction and TOR signaling.[2] A critical next step will be to determine how altered vacuolar dynamics impact aging.

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Metformin is synthetically lethal with glucose withdrawal in cancer cells

Comment on: Menendez JA, et al. Cell Cycle 2012; 11:2782–92; PMID:22809961; http://dx.doi.org/10.4161/cc.20948

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In a recent issue of *Cell Cycle*, Menendez and colleagues proposed a novel concept, that metformin is synthetically lethal with glucose withdrawal in cancer cells.[1] Historically, synthetic lethality has focused on how tumor cells are responsive to certain agents that only harbor specific constitutive epigenetic or genetic lesions.[2] More recent data from several groups have uncovered that altered tumor microenvironment could be used to confer synthetic lethality to specific drugs, defined as "contextual synthetic lethality," that is microenvironment-mediated. For example, hypoxia-induced HR (homologous repair) defect has been shown to be synthetically lethal to PARP inhibition, while PARP inhibition, per se, did not alter HR inhibition or function, thus providing a prime example of "contextual synthetic lethality."[3] In this report, Menendez et al. have elegantly connected the glucose-deprived tumor microenvironment in primary tumors as a synthetic lethal partner to metformin. Metformin is a FDA-approved drug to treat diabetic patients that is gaining momentum as a repurposing drug for cancer treatment.[4] Using several different breast cancer cells with and without oncogenic activation, the authors have shown that the glucose-rich conditions of the in vitro experiments dictates the use of very high concentrations of metformin, which are not applicable to glucose-starved in vivo conditions. While other reports have alluded to the effect of glucose withdrawal in killing genetically compromised cells to therapeutic effect of metformin in vitro,[5] Menendez et al. have provided a logical explanation for the use of very high concentrations of metformin to achieve anticancer effects in vitro in the high glucose-rich environment used in these experiments, which are clinically not applicable in vivo in patients.

Based on these findings, it can be envisaged that in the tumor microenvironment, where the cancer cells are under extreme nutritional and hypoxic stress (a niche for cancer stem cells), metformin treatment could favor synthetic lethality and hence effectively can attenuate tumor growth. The tumor microenvironment thus enables the bioenergetic switch in favor of glycolysis and dependence on glucose and glutamine as a rapid source of nutrition. While the authors' data clearly depicts how metformin eliminates the tolerance of the breast cancer cells to fluctuations in glucose concentrations, it is important to understand how the availability of other dominant sources of energy, such as glutamine, might participate in this scenario. It is plausible that subtype of breast cancers, i.e., basal vs luminal, might depend on different energy source, albeit to a different extent.[6] This is important, because tumor cells often acquire metabolic adaptability toward available preferred energy source to adapt well to nutritional stress via autophagy and altered metabolism.[7] Along these lines, the authors rationalize the therapeutic targeting of the cancer stem cells by metformin through its synthetic lethal activity to the hyperglycotic phenotype often seen in CSC to sustain their stemness.[8] Further characterization of how metformin treatment alters the metabolic nodes in cancer stem cells and/or p53-null cells would explain the underpinning mechanisms for increased susceptibility of these indolent and aggressive cancer cells toward metformin.

It is well documented that metformin, by inhibiting complex I of respiratory chain in mitochondria (ETCI), induces a decrease in the ATP levels, and that glucose depletion also decreases ATP levels, albeit to varying levels. Therefore, it is possible that simultaneous

targeting of both pathways (glycolytic pathway and OXPHOS) caused ATP depletion below a critical threshold, resulting in cell death. This concept is supported by the elegant study[9] highlighting the effectiveness of combination of glycolysis inhibition by 2-DG and metformin in several preclinical models exhibiting anti-tumor effects, including MB-MDA231 used in this study.

Since recent studies indicate that inhibiting glucose uptake with small-molecule inhibitors led to a decline in cylcin E2 and p-RB levels,[10] it is a possibility that cell cycle inhibitor levels are also regulated under glucose withdrawal conditions, sensitizing cells to cytotoxic effects of metformin in breast cancer cells.

Considering data from several studies, a view that metformin treatment has pleotropic effects on several signaling pathways under glucose-free conditions seems a practical possibility. Overall, this work offers several new insights into glucose-dependent mechanisms underpinning the mode of action of metformin as a viable therapeutic strategy.

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Lin28 and HER2: Two stem cell regulators conspire to drive aggressive breast cancer

Comment on: Feng CN, et al. Cell Cycle 2012; 11;2486–94; PMID:22713243; http://dx.doi.org/10.4161/cc.20893

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Approximately 20% of human breast cancers overexpress the HER2 gene, a state that is associated with an aggressive clinical course with high metastatic propensity. The development of HER2 targeting agents such as trastuzumab have greatly improved the outcome for these patients, representing one of the most successful molecularly targeted therapies. Although HER2 protein overexpression usually results from gene amplification, this is not always the case, and it is unclear what accounts for increased HER2 protein expression in these cases. Reporting in *Cell Cycle*, Feng et al. demonstrated a significant association of Lin28 expression with the expression of HER2, both of which were associated with poor clinical outcome.[1] Lin28 was originally described as a gene regulating developmental timing in worms.[2] Lin28 directly modulates the expression of a number of genes post-transcriptionally.[3] Feng et al. demonstrated that Lin28 binds to target sites present in HER2 mRNA, leading to enhanced HER2 protein expression. This confirmed a prior study, which reported that Lin28 was overexpressed in HER2-positive breast cancers.[4]

Lin28 is known to be an important stem cell regulatory gene. In fact, it is one of four factors sufficient to reprogram human somatic cells into induced pluripotent stem cells.[5] More recently, Lin28 has been found to have profound effects on normal and malignant stem cells through the posttranscriptional downregulation of the microRNA Let-7. The inverse regulatory relationship between Lin28 and Let-7 microRNA has been well documented during normal development, cell metabolism and tumorigenicity. On the one hand, Let-7 negatively regulates stemness by repressing self-renewal and promoting differentiation in normal development and cancer, while Lin28 is expressed at higher levels in undifferentiated cells and decreases during cellular differentiation. Lin28 has been reported to function as an oncogene that promotes cellular transformation, an effect that was abrogated by expression of Let-7.[6] In breast cancer cells, endogenous levels of Let-7 mRNAs were found to be markedly reduced in mammospheres and in cancer stem cells that displayed a CD44+/CD24- phenotype, while levels were significantly increased in more differentiated cells forming the tumor bulk.[7] Expression of Let-7 in breast cancer stem cells inhibited their capacity for self-renewal and induced differentiation, while downregulation of Let-7 in differentiated cells promoted their de-differentiation and acquisition of CSC properties. Lin28 and Let-7 have also been shown to be involved in sustaining an inflammatory feedback loop involving interleukin-6 and NFκB, a loop that drives the breast cancer stem cell population (see **Fig. 1**).

Our laboratory and others have also implicated the HER2 gene in the regulation of breast cancer stem cells. This occurs through activation of the Wnt pathway through GSK3B and β-catenin phosphorylation.[8] Overexpression of HER2 in normal mammary epithelial cells and mammary carcinomas increases the population of CSCs, a state associated with increased CSC self-renewal and tumorigenicity. Loss of PTEN function in these cells generates a trastuzumab-resistant CSC population through activation of an IL-6 inflammatory loop involving NFκB. This is associated with generation of an epithelial-mesenchymal transition (EMT) invasive phenotype. NFκB plays an essential role in HER2 induced oncogenesis by providing signals that maintain mammary tumor-initiating cells.[9] The observation that HER2 can regulate NFκB,[10] and that NFκB can regulate Lin28,[11] coupled with the report of Feng et al. that Lin28, in turn, regulates HER2 suggests that these two important stem cell regulatory genes may interact in a positive feedback loop (see **Fig. 1**).

Lin28 is one of the vital factors in the networks of different regulatory elements that

may be responsible for the elevated HER2 expression in a subpopulation of cells in HER2 non-amplified tumors. These networks also involve multiple CSC regulators such as HER2, Akt, NFκB and IL-6. As illustrated in **Figure 1**, targeting these pathways may reduce the CSC population improving patient outcomes.

Disclosures

Max S. Wicha is a scientific advisor and holds equity in Oncomed Pharmaceuticals and is a scientific advisor for Veristem.

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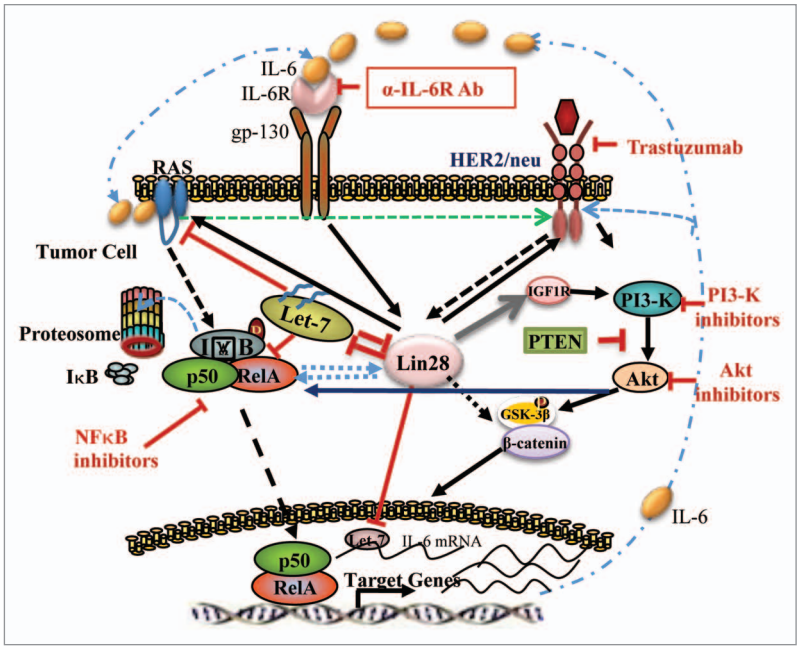

Figure 1. Interaction of Lin28 and HER2 signaling pathways. Lin28 and HER2 interact to regulate cancer stem cells. Potential inhibitors of these pathways are shown.