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News and Commentary

# Do cells need CDK2 and…Bcr-Abl?

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## Paradox of CDK2

Until recently, the central role of CDK2 in the G1/S transition was unshakable dogma. Even a recent publication noting that CDK2 activity is not necessary for proliferation of cancer cells was not terribly surprising.[1] In cancer cells, alterations in tumor suppressors and oncogenes result in loss of the restriction point of the cell cycle.[2–4] Thus, for example, overexpression of E2F and c-Myc alone can drive G1/S progression.[5,6] It was predicted that some cancers do not need CDK2 or CDK4 and that inhibitors of CDKs can be used for selective growth arrest in normal cells.[7,8] However, a conclusion by Ortega *et al.*[9] and Berthet *et al.*[10] that CDK2 is not needed for any somatic cells was unexpected.[11–15] CDK2-knockout mice develop normally and their cells proliferate in culture. Furthermore, cyclins E1 and E2, CDK2 activators, are not needed for embryonic development.[16] On the other hand, inhibitors of CDK2, both natural (p21 and p27) and synthetic anticancer agents, inhibit proliferation in most cell lines.[17–18] It could be argued, however, that these inhibitors are not selective for CDK2 and affect other targets. So in the end, does a cell need CDK2 or not? Here, I discuss a third way, exemplified by the Bcr-Abl fusion protein.

## The Bcr-Abl network

Successful treatment of Bcr-Abl-expressing leukemia with the Bcr-Abl kinase inhibitor Gleevec (imatinib, STI571) is the most spectacular achievement in oncology.[19–21] Bcr-Abl, a product of a chromosomal translocation resulting in the Philadelphia chromosome, is specific and vital for leukemia. In leukemia cells, Gleevec causes apoptosis, cell death mediated by caspases.[20–23] When apoptosis is blocked by caspase inhibitors, cells get arrested in G1.[22] Thus, Bcr-Abl inhibits apoptosis and induces G1/S transition.[24–27] Bcr-Abl blocks caspases and activates CDKs by several mechanisms (Figure 1). Bcr-Abl induces HSP70, which blocks apoptosis.[28–29] Bcr-Abl activates STAT-5 and NF-kB transcription factors, which in turn induce BclxL and IAP.[26,30–32] Bcl-xL blocks the mitochondrial apoptotic pathway, while IAP blocks caspases (Figure 1). Also, Bcr-Abl activates Ras and the PI3K/Akt pathway, which inhibit apoptosis and stimulate proliferation.[32–34] Ras, PI-3K and STAT-5 induce cyclin D1 and D2.[35–37] Cyclins D activate CDK4/6, which by releasing E2F transcativates cyclin E. Cyclin E activates CDK2, and Bcr-Abl causes relocation of p27 to the cytoplasm, further stimulating CDK2.[38]

## Paradox of Bcr-Abl

It seems to be expected that Gleevec causes growth arrest and apoptosis in Bcr-Abl-expressing cells. What is surprising, although, is that Bcr-Abl, an unintended product of chromosome translocations, is absolutely dispensable; all normal cells live well without Bcr-Abl. For example, HL60 cells proliferate and live in the presence of Gleevec.[22,23,28,39] This is not unexpected: not only do HL60 cells not have Bcr-Abl, they do not need it. However, we still can trasfect HL60 with Bcr-Abl, of course. How will Gleevec affect such Bcr-Abl-transfected HL60 cells? From common sense, we can expect that Gleevec will do nothing. After all, HL60 cells do not need Bcr-Abl. Counterintuitively, Gleevec induces apoptosis and growth arrest in Bcr-Abl-expressing HL60 cells.[22,23,28,39] This is not a negligible phenomenon, and allows one to cure leukemia.

## The Bcr-Abl dam model

In the absence of Bcr-Abl, multiple activators and inhibitors of apoptosis (not shown for simplicity, Figure 2) regulate the caspase cascade (Figure 2a). As we discussed (Figure 1), Bcr-Abl blocks several steps of the apoptotic cascade (Figure 2b, shown for simplicity as one step). If proapoptotic stimuli act upstream of the Bcr-Abl block, then they do not cause apoptosis. In fact, Bcr-Abl-expressing cells are resistant to apoptosis caused by most anticancer agents, including DNA-damaging and microtubule-active drugs.[23,24,39–41] Therefore, proapoptotic molecules may accumulate upstream of the Bcr-Abl block. In the presence of Bcr-Abl, other inhibitors of apoptosis become redundant. For example, Bcl-2 is downregulated because it is substituted for by BclxL, which is induced by Bcr-Abl,[23,42,43] and when caspases are inhibited, there is a compensatory increase in levels and activity of upstream apoptotic pathways, because caspases are involved in cellular functions beyond apoptosis (Figure 2b). Like a stream blocked by a dam, the apoptotic pressure can accumulate upstream of Bcr-Abl. If the Bcr-Abl dam is suddenly removed, the apoptotic cascade will be activated (Figure 2c). Similarly, inhibition of Bcr-Abl will eliminate a driving force in the cell cycle, such as Bcr-Abl-activated CDK2. Thus, it is a *sudden* inactivation of growth promoting and survival proteins (e.g., CDK and Bcr-Abl) that causes growth arrest and cell death. Like cells lacking Bcr-Abl (normal cells), CDK2-knockout cells can progress through cell cycle. However, in natural cells, CDK2 is involved in G1/S progression. Its sudden inhibition by p27, for instance, results in cell cycle arrest. CDK2 is conditionally dispensable for cell

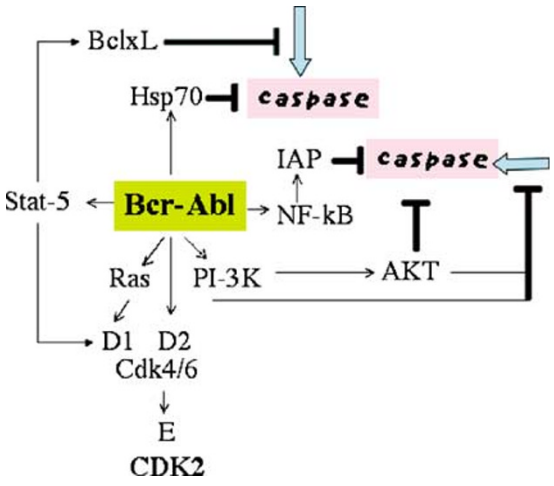


**Figure 1** Bcr-Abl inhibits apoptosis. By multiple mechanisms, Bcr-Abl inhibits caspases and activates CDKs

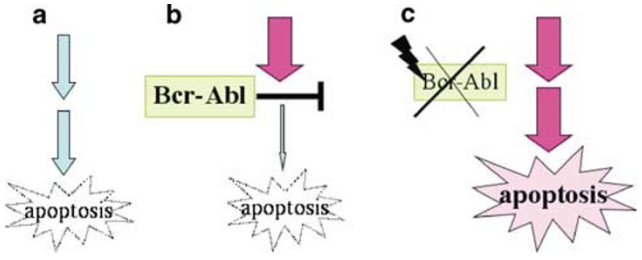


**Figure 2** The dam model. (**a**) Normal cells; apoptotic cascade. (**b**) Bcr-Abl-expressing cells. Bcr-Abl blocks apoptotic pathways. While upstream pathways are active, downstream pathways are not. Levels and activity of upstream apoptotic pathways may be compensatorily increased. (**c**) Sudden inactivation of Bcr-Abl; removal of the dam activates downstream pathways and causes apoptosis

cycle. If CDK2 is not expressed, it is not needed. However, if CDK2 is expressed, it is engaged in the G1/S progression and is not dispensable at that particular moment, at least in some types of cells.

## Cdk2: clinical applications

Gleevec induces growth arrest and cell death in Bcr-Abl-addicted leukemias. In analogy with Gleevec, inhibitors of CDK2 will arrest cancer cells that are addicted to CDK2. These cancers may be treated with CDK2 inhibitors alone. In CDK2-dependent tumors, CDK2 inhibitors may cause cell senescence. In the presence of overactivated mitogenic signaling (e.g., ErbB, Ras, Raf), unscheduled inhibition of CDKs may induce senescence.[44] In the presence of elevated E2F, associated with cancer, inhibition of CDK2 can lead to apoptosis.[45]

Given recent findings,[1,9–16,46] there is no reason to think that CDK2 is *universally* needed to all normal cells. Likely, certain types of normal cells are CDK2 independent. At present, we do not know which types of cells (e.g., hematopoietic cells, colon epithelial cells, hair follicular cells) are CDK2 dependent or not. CDK2-independent normal cells

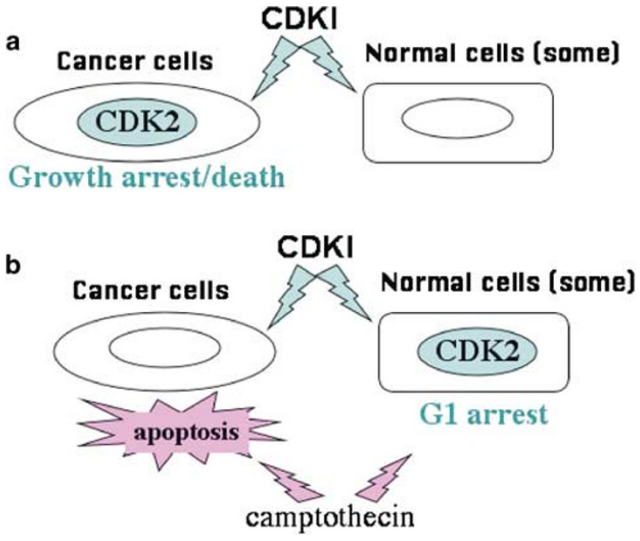


**Figure 3** Two strategies of CDK inhibitors in cancer therapy. (**a**) In CDK2-dependent cancers, monotherapy with CDK2 inhibitors (CDKI) will block proliferation of cancer cells. Since some normal cells are CDK2 independent, there will be fewer side effects than previously anticipated. (**b**) In therapy of CDK2-independent tumors, CDK2 inhibitors may be used as modulators of the cytotoxicity of chemotherapy, because some normal cells are CDK2 dependent. Pretreatment with CDK2 inhibitors (CDKI) will arrest proliferation of these normal cells. Then, a cycle-dependent drug, such as camptothecin, will kill proliferating cells, without killing cells arrested by CDKI

will not be affected by CDK2 inhibitors (Figure 3a). This has far-reaching consequences: there will be less side effects than previously anticipated.

On the other hand, at least some tumors are CDK2 independent.[1] Certain cancer cells are insensitive to both endogenous and pharmacological inhibitors of CDKs. For therapy of such cancers, CDK2 inhibitors can be used too, yet for a different purpose: namely, for protection of normal cells from chemotherapy. Pretreatment with CDK2 inhibitors may induce G1 arrest in some normal cells, rendering these cells insensitive to chemotherapy that kills proliferating cells (Figure 3b). This potentially will decrease side effects of chemotherapy.[47,48]

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