Meeting Report

1994 Forbeck Cancer Forum on Cell Cycle Checkpoints

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The 1994 Forbeck Cancer Forum on Cell Cycle Checkpoints met at Hilton Head Island, South Carolina, October 27–29. Contributors included scientists working on yeast cell cycle (Steven Elledge, Leland Hartwell, and Kim Nasmyth), mammalian cell cycle (Ed Harlow, Patrick O’Connor), DNA repair (Richard Kolodner), apoptosis (Gerard Evan), pharmacology (Herbert Newell), tumor development in animal systems (Terry Van Dyke), clinical science (Karen Antman, Fred Applebaum, Brian Reid), and the “big picture” (Steven Friend). Two and a half days of discussion focused on our current understanding of cell cycle checkpoints and how this knowledge might eventually be implemented for cancer prevention and therapy.

A remarkable number of cell divisions occur during a normal human life span. Perhaps $10^{16}$ or $10^{17}$ cell divisions take place by the time an adult reaches mid-life, and almost all of them occur in an orderly manner. This orderly division is controlled by many different mechanisms, but one of the most important is the regulation imparted by the cell cycle checkpoints. These checkpoints can be viewed as safety monitoring mechanisms that evaluate whether the cell should proceed with its next step in the division cycle, or whether it should wait until some needed repairs are completed. Loss of this monitoring surveillance systems can lead to disruption of orderly division, and it now is clear that these losses play an important role in the genesis of many, and perhaps all, cancers.

A cell’s decision to divide is one of several options that it has. Other options include the decision to differentiate or to die. All of these options are ultimately directed by extracellular cues that signal a cell about its appropriate response. These signals take many forms, but eventually they impose actions at key time points of a cell division cycle. These decision times have become known as transition points, and molecular changes at these transition points commit the cell to proceed to the next stage of the division cycle. The molecular events that drive these transitions are the activation of particular cell kinases. The best characterized transition points are the commitment to enter DNA synthesis and the commitment to begin mitosis. These two transition points are also the times at which the cell cycle checkpoints monitor correct completion of previous events in the cycle. Unlike the external cues that indicate what decisions a cell should make, the checkpoint signals are intracellular. They impose a block on the transition point and alert the cell that it should not proceed until some corrective measure is complete. When these checkpoint monitoring systems are operating correctly, they allow various damage control, repair mechanisms, or safety checks to be completed before proceeding.

Normally these checkpoints are initiated correctly and help a cell respond to some unexpected stress. The stress is recognized, the correct response is initiated, and the cell can continue its division cycle normally. When the checkpoints themselves are disarmed by mutation, cell division normally proceeds without undue change. However, when cells with damaged checkpoint controls are stressed unexpectedly, they no longer can respond correctly and damage may result in permanent changes in the affected cells. If these changes are in key proliferation controls, they will contribute to the loss of control seen in tumor cells.

Loss of checkpoint controls are common in cancer cells, and are probably responsible for their rapid evolution through genomic instability. Drugs that could restore lost checkpoint function, either by reactivating a protein like p53 or inactivating proteins responsible for its down-regulation, like MDM2 could be important in cancer prevention. Checkpoint controls are also responsible for the ability of cells to withstand DNA or spindle damage commonly employed during radio- and chemotherapy. Drugs that inactivate checkpoints could enormously enhance the efficacy of these treatments. Moreover, since tumor cells are frequently missing certain checkpoints they may be more vulnerable to the loss of other checkpoints than are normal cells. If so, such a strategy could provide a large therapeutic index.

Although these ideas appear promising, other factors that weigh against rapid implementation are the enormous complexity of cell cycle controls, the limited knowledge now available, and the diversity of cancer as a disease. We do not know the number of different kinds of tumors that can arise from an organ, the normal cells they arise from, the number of genetic pathways to tumorigenesis, or the genetic diversity present once a tumor has become malignant. We do not have appropriate normal cells to compare tumor cells with in experiments. The conditions that we use to culture tumor cells in vitro suppress the normal apoptotic response which may be critical in eradicating tumors. With an initial load of $10^9$ or $10^{12}$ tumor cells at the time of detection, it will be extremely difficult to kill all cells, and even rare survivors can result in recurrence of disease. We know very little about how cells die in response to chemotherapy. In the area of cell cycle control, we do not know the targets of the cyclin-dependent kinases and have little in the way of methods for finding them. It is clear that functional redundancy as well as elaborate positive and negative feedback loops are operative in cell cycle control pathways, making it nearly impossible to predict the outcome of inhibiting a specific step.

Clearly, we need to continue the process of defining cell cycle controls and pathways of cell death. We need more data from in vivo systems on cell proliferation, death, and response to therapeutic intervention. We need to take empirical approaches to determining the consequences of target inhibition in cells. We need to screen for therapeutic agents in whole cells as well as with defined protein targets for the desired end point, cell death.
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