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dred kilometers north of the float experiment, do indicate the presence of cyclonic motion below the steady plume level (*7*), suggesting that a similar situation may occur at the Gorda Ridge. Thus, very different float trajectory behavior can be expected near the formation site of an event plume at different depths, and a float may drift from one type of circulation regime to another if multiple plumes are forming.

In a larger context, ridge-related oceanography has experienced a renaissance as the effect of fracture zones and passages on the control of deep and bottom water, the evidence for enhanced mixing above the flanks of the ridge, and the possible role of this mixing as well as geothermal heating on deep upwelling all occupy the attention of researchers. The propagation of event plumes adds another element to the impact of the ridge on deep circulation and the transport of volcanically enriched seawater and hydrothermal organisms. Much remains to be done to quantify this transport, and floats will clearly be of help because they mark water parcels approximately and in principle reflect the net effect of all transport processes from mean and fluctuating currents. Transport in the across-ridge direction by event plumes is of special interest; flow along the ridge may be dominated by the combined effects of many weaker, nearly steady sources of heat, as well as nonhydrothermal effects. Future experiments are likely to be cross-disciplinary, already a notable aspect of hydrothermal research, involving a diverse set of measurements to address mixing and transport issues related to geothermal heating, internal-gravity wave breaking, and the role of topographic waves on the ridge flank and crest. These physical processes all exert some control on circulation and, in turn, water column chemistry is helping to provide information about the circulation not only with tracers but also with quantitative constraints on residence times, turbulent suspension velocities, and the nature of heat and chemical transfer at the source.

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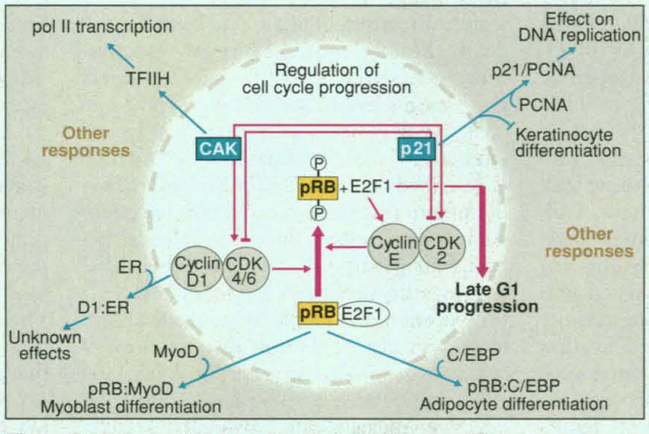
CELL CYCLE

The Expanding Role of Cell Cycle Regulators

Tyler Jacks and Robert A. Weinberg

The cell cycle clock orchestrates the progression of eukaryotic cells through their growth and division cycles. Much of its importance derives from its job as the master controller of a cell's decision to continue proliferating or to withdraw from the cycle and enter a state of quiescence. But recent work—including that of Di Cunto *et al.* on page 1069 of this issue (*1*)—points to a wider role for components of the clock apparatus, some of which extend their reach as far as cellular differentiation.

The core clock machinery is assembled from modular components—cyclins and cyclin-dependent kinases (CDKs). The CDKs control various cellular responses through their ability to phosphorylate appropriate substrates within the cell. The cyclins, acting like guide dogs, bind to and direct CDKs to appropriate substrates during specific phases of the cell cycle, thereby dictating when and where these substrates will become phosphorylated.



The cell cycle machinery extends its influence. ER, estrogen receptor; pRB, retinoblastoma protein; p21, cyclin-dependent kinase inhibitor; E2F1, transcription factor active in late G_1 phase; MyoD, transcription factor controlling muscle differentiation; CAK, CDK-activating kinase; C/EBP, transcription factor controlling adipocyte differentiation.

The retinoblastoma protein, pRB, and related family members are critical targets for cyclins and CDKs. During the mid-G_1 phase of the growth cycle, their phosphorylation by certain cyclin D–CDK4 and cyclin D–CDK6 complexes enables the activation of yet other cyclin-CDK complexes and the transcription of genes required for S phase entry and progression. All these events permit the cell to advance into the late G_1 and S phases (see the figure).

Equally important components of this core machinery are two groups of CDK inhibitors (CKIs) that block the actions of specific cyclin-CDK complexes (green squares in the figure). In so doing, they may prevent cell cycle progression or induce cells to exit the active proliferative cycle and enter the quiescent G_0 phase. For example, CKIs of the INK4 group (p15, p16, p18, p19) are specialized to block the cyclin-CDK4 and cyclin-CDK6 complexes that are essential to pRB phosphorylation and the associated advance into the late G_1 phase of the cell cycle.

But some of the components of the cell cycle clock have other functions besides direct control of proliferation. The Di Cunto *et al.* report indicates that the p21 CKI, which is capable of inhibiting a wide spectrum of CDKs operating throughout the cell cycle, also participates in the development of differentiated phenotypes of keratinocytes of the skin. These authors demonstrate that the amount of p21 protein decreases as keratinocytes initiate end-stage differentiation, and that forced expression of p21 can inhibit the differentiation process. Biochemical and mutational evidence indicates that this differentiation-inhibiting function of p21 can be

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separated from its abilities to inhibit cyclin-CDK complexes (*1*).

An early precedent for a double life for CKIs has come from the Far1p protein of the budding yeast *Saccharomyces cerevisiae*. Originally discovered as a CKI induced by mating pheromones, Far1p was later shown to have a distinct function: orienting the yeast cell toward its mating partner (*2*, *3*). Similarly, the mammalian p21 protein studied by Di Cunto *et al.* has another personality, a domain capable of binding to the PCNA (proliferating cell nuclear antigen) component of DNA polymerases, thereby affecting the process of DNA replication (*4*, *5*). This function of p21 outside of the core clock machinery provides an additional precedent for a multifunctional CKI that can affect cellular targets other than the core components of the clock machinery.

Other surprises of this sort have emerged recently. Cyclin D1 was initially portrayed as an important activator of the CDK4 and CDK6 complexes that phosphorylate pRB and related proteins in the G_1 phase (*6*). But reports from two groups indicate, totally unexpectedly, that cyclin D1 can bind and activate the estrogen receptor (ER) (*7*, *8*). Before this work, estrogen was thought to be the major physiologic activator of this receptor. The biological consequences of the cyclin D1–ER interaction remain unclear; given the wide-ranging actions of the ER, some of them might involve differentiation-like responses.

pRB has been portrayed exclusively as the brake shoe of cell cycle advance in the G_1 phase of the growth cycle; its absence or functional inactivation in many types of human tumors is compatible with this action (*9*). But new research indicates that pRb helps to direct the development of at least two distinct differentiation programs. Cultured myoblasts do not differentiate properly in the absence of pRB (*10*, *11*). This differentiation function appears to be associated with a domain of pRB that is distinct from those domains that directly control proliferation (*12*). Yet other work indicates an analogous role for pRB in programming adipocyte differentiation (*13*). Although these results stem from in vitro differentiation models, we suspect that they reflect processes operative in living tissues and that the differentiation programs in a variety of other tissues may be similarly dependent on pRB function.

A particularly intriguing example of an intrinsic cell cycle regulator moonlighting in another cellular function is the CDK-activating enzyme CAK, a kinase required for the full stimulation of CDK activity. In mammalian cells, CAK is also a critical component of the RNA polymerase holoenzyme (its TFIIH subunit), required for the transcription of most cellular genes (*14*–*16*). Whether this is an example of a cell cycle regulator being coopted by evolution to perform a transcriptional function or the reverse is not known.

The portrait of the cell cycle clock as an apparatus focused exclusively on governing proliferation has become simplistic. It now seems clear that this apparatus, embedded in the heart of the eukaryotic cell for a billion years, has been exploited by the tinkering hand of evolution to control other important cellular functions, particularly those that are required for complex cellular differentiation. Evolution, always opportunistic, uses the hardware already lying around on the shelves to make clever new toys. The powers of the cell cycle clock apparatus are likely to be far broader than currently suspected.

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ONCOGENESIS

Landscaping the Cancer Terrain

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Few lines of investigation have taught us more about cancer than the study of inherited tumor susceptibility syndromes. Initially, the mutations responsible for these diseases were thought to promote malignancy in a straightforward manner, through inactivation of "tumor suppressor" genes, which directly modulate cell birth or cell death. More recently, however, susceptibility genes that work through less-direct mechanisms have come to light. The genes defective in patients with juvenile polyposis syndromes (JPSs), for example—one of which is described on page 1086 of this issue (*1*)—illuminate this principle and also raise fundamental questions about the relation between neoplastic cells and the "other cells" that together constitute a tumor mass.

A dozen tumor suppressor genes are known to prevent cancer through direct control of cell growth—including *p53*, *Rb*, *VHL*, and *APC*. Inactivation of these genes contributes directly to the neoplastic growth of the tumor; thus, they normally function as "gatekeepers" to prevent runaway growth (see the figure). Accordingly, restoration of the missing gatekeeper function to cancer cells leads to suppression of the neoplastic growth.

These traditional tumor suppressors are being joined by an ever-increasing number of susceptibility genes that indirectly suppress neoplasia (for example, *XPB*, *ATM*, *MSH2*, and *MLH1*). The prototypes for this class of genes encode DNA repair proteins that act as "caretakers" of the genome. Inactivation of a caretaker gene results in a greatly increased mutation rate and is equivalent to a constant exposure to mutagens. It is not surprising that such defects should lead to cancer, but restoration of caretaker function to a cancer cell will not affect its growth. As these indirectly acting genes are never *required* for neoplasia, most nonhereditary (sporadic) tumors will evolve without them.

A second class of indirectly acting cancer susceptibility genes is suggested by recent studies on JPS. Individuals with JPS have an increased risk of colorectal cancer, but the primary manifestation of this syndrome is the development of multiple hamartomatous polyps of the colon at a young age. These polyps are markedly different from the epithelium-rich adenomatous polyps that give rise to most cases of colorectal cancer. Polyps from patients with JPS have a low potential to become malignant and are composed largely of stromal cells, comprising a mixture of mesenchymal and inflammatory elements in which epithelium is entrapped, often forming dilated cysts. The epithelial cells within and surrounding the polyp are initially devoid of neoplastic features but nevertheless are at increased risk of becoming malignant.

It would thus seem that the increased cancer susceptibility due to inherited mutations in JPS is the product of an abnormal stromal environment. That an abnormal stroma can affect the development of adjacent epithelial cells is not a new concept. Ulcerative colitis

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