PERSPECTIVES: CELL CYCLE

Order from Destruction

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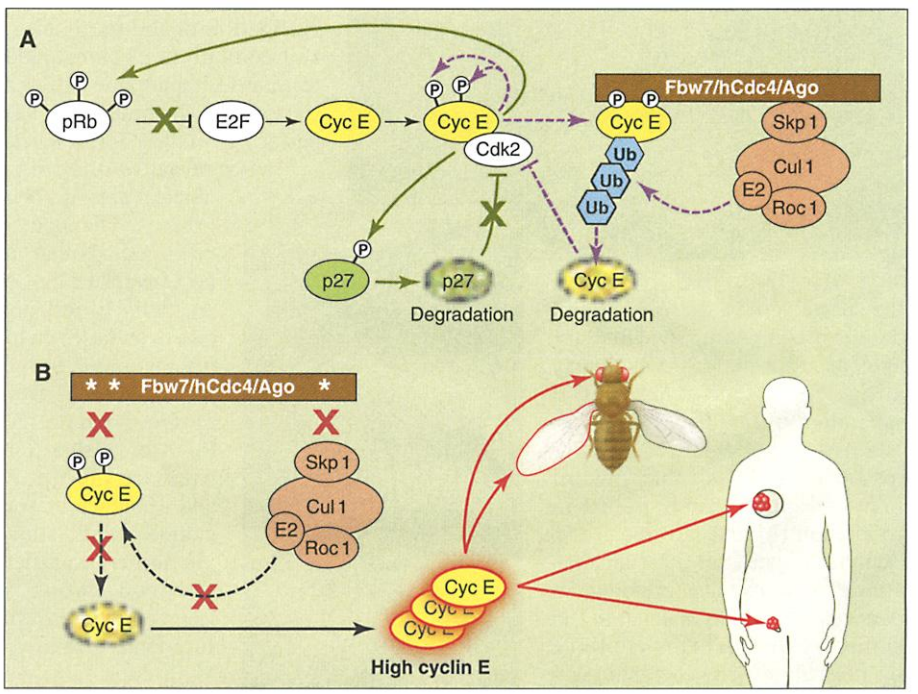
To guard against developmental defects and devastating diseases such as cancer, all cells great and small have evolved ways to exert tight control over the protein machinery that regulates the cell cycle. Modulating the abundance of proteins such as cyclins that are crucial for progression through the cell cycle is one means by which cells control their proliferation. The successive rise and fall of individual cyclins during each cell cycle is achieved primarily by alternating their timely transcription with their proteasome-dependent degradation. This dual control ensures that each cyclin reaches the threshold necessary to activate its catalytic partner, a cyclin-dependent kinase (CDK), during the correct phase of the cell cycle. For example, cyclin E is low in early G_1, rises to a peak in late G_1, activates CDK2 around the G_1-S transition, and falls again during the S, G_2, and M phases of the cell cycle. This expression profile reflects the importance of the cyclin E–CDK2 complex in promoting the initiation of genome replication during S phase. Careful control of cyclin E abundance and the activity of its associated kinase is essential for the timely onset of DNA synthesis. Insufficient cyclin E results in cell arrest in G_1, whereas too much cyclin E leads to premature entry into S phase, genomic instability, and the formation of tumors (*1*–*3*).

Given its critical involvement in the control of cell proliferation and the development of cancer, elucidating the regulation of cyclin E turnover has remained high on the wish list of cell cycle researchers (*4*). Discoveries reported on page 173 of this issue (*5*) and in two recent *Nature* papers (*6*, *7*) identify the "missing link": the key protein that targets cyclin E for destruction. This protein—called Fbw7 or hCdc4 in humans, and Archipelago (or Ago) in flies (*5*–*7*)—belongs to a large family of so-called F-box proteins (*4*). F-box proteins are adaptors that form a bridge between a substrate (in this case cyclin E) and SCF, a ubiquitin ligase composed of several subunits that is part of the proteasomal degradation pathway (see the figure). The addition (ligation) of ubiquitin residues to substrate proteins is the signal for their rapid degradation by the 26*S* proteasome, a multisubunit cellular factory that specializes in the unfolding and proteolysis of ubiquitin-tagged proteins (*8*). Individual F-box proteins bind to a particular phosphorylated substrate at a precise moment of the cell cycle, and simultaneously bring this substrate into the vicinity of the SCF ubiquitin ligase. The result is a time- and target-specific machine that quickly degrades certain proteins and thus modulates important regulatory processes in the cell.

What is so exciting about this new F-box protein, and what are the implications of its discovery? First, the complementary cellular systems used by the discoverers of Fbw7/hCdc4/Ago reveal that it is highly conserved, from worms and flies to humans, a sign of its importance. Second, the involvement of Fbw7/hCdc4/Ago in cyclin E turnover provides insights into the regulatory circuitry that monitors oscillations in cyclin E–CDK2, an essential activity that, if defective, is hazardous to the cell (see the figure). The identification of Fbw7/hCdc4/Ago confirms that free cyclin E and phosphorylated cyclin E bound to CDK2 are targeted for degradation by different pathways (*4*). In addition, the identification of Fbw7/hCdc4/Ago will help to elucidate the molecular basis of the more common cyclin E–CDK2 degradation pathway. The dramatic eye and wing phenotype seen when Ago is mutated in fruit flies (*7*) further emphasizes the need to keep a precise balance of cyclin E



Keeping the balance. (**A**) Under normal growth conditions, cyclin E regulates its own abundance. The cyclin E–CDK2 kinase complex promotes cyclin E synthesis by phosphorylating and inactivating the pRb repressor of E2Fs, transcription factors that stimulate cyclin E expression (*10*). Cyclin E–CDK2 also phosphorylates p27, thereby priming this powerful inhibitor of CDK2 for rapid destruction (*11*). As a result, the cell achieves a sharp peak of cyclin E–CDK2 activity, which is necessary for the initiation of genome duplication during S phase. The negative feedback loop relies on autophosphorylation of cyclin E by CDK2. The two resulting phosphates in cyclin E create a landing pad for the newly discovered F-box protein, Fbw7/hCdc4/Ago (*5*–*7*). This protein links cyclin E with the SCF ubiquitin ligase composed of the Skp1/Cul1/Roc1 subunits. Together, the SCF complex and the ubiquitin conjugase (E2) catalyze the addition of ubiquitin chains to cyclin E, thereby marking it for destruction. Cyclin E destruction through the proteasome-degradation pathway inhibits cyclin E–CDK2 activity after its mission has been completed. (**B**) Mutations in Fbw7/hCdc4/Ago (asterisks) disable its ability to recognize phosphorylated cyclin E or to interact with SCF, generating an imbalance in cyclin E–CDK2 autoregulatory circuits. Such an imbalance may lead to uncontrolled cyclin E accumulation and the dramatic consequences of excessive cell proliferation. Disruption of Ago in flies leads to developmental eye or wing defects (*7*); mutations in the gene encoding human Ago/hCdc4 may predispose individuals to breast or ovarian cancer (*6*, *7*).

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throughout development (see the figure). The next challenge is to understand how Fbw7/hCdc4/Ago is itself regulated and where it interacts with cyclin E in the cell. The issue of space is puzzling because cyclin E appears to have an exclusively nuclear location, whereas Fbw7/hCdc4/Ago has a transmembrane domain (*5*) suggesting that it is restricted to cellular membranes. By following the subcellular trafficking of cyclin E in living cells in real time, it should be possible to pinpoint where cyclin E and Fbw7/hCdc4/Ago interact. It will be important to work out the exact timing of cyclin E destruction: Is cyclin E continuously degraded, or is it only degraded after its mission has been completed?

Arguably, of greatest importance is the finding that mutations in Fbw7/hCdc4/Ago implicate this F-box protein in the pathogenesis of some forms of human breast and ovarian cancer (*6, 7*). Mutations prevent Fbw7/hCdc4/Ago from targeting cyclin E for ubiquitin-mediated degradation (see the figure), resulting in aberrantly elevated cyclin E, which promotes uncontrolled cell proliferation leading to cancer. Such loss-of-function mutations are a hallmark of a group of cancer-associated proteins termed tumor suppressors, and Fbw7/hCdc4/Ago qualifies for membership in this group. Interestingly, the cyclin E gene itself is overexpressed in many types of tumors (*9*) and belongs to the other major group of cancer-associated genes, the proto-oncogenes, which contribute to tumor formation through their excessive activity. Thus, there is a dark side to the interplay between cyclin E and Fbw7/hCdc4/Ago, as both are encoded by "dormant" cancer genes.

The cancer defects associated with Fbw7/hCdc4/Ago mutations shed new light on the mysterious finding that certain tumors including some breast tumors have elevated cyclin E protein in the absence of increased cyclin E gene amplification or mRNA production. In addition, the tumor suppressor protein pRb guards the transcription of cyclin E, and another tumor suppressor, the inhibitor p27, blocks cyclin E–CDK2 activity (see the figure) (*10, 11*). Collectively, aberrant forms of these proteins share the ability to promote overactivity of cyclin E–CDK2, and thus may have similar consequences: the deregulated growth of cells leading to cancer. Pinpointing precise defects within this delicate molecular machinery will help in the design of improved cancer therapeutics. It is encouraging that both inhibitors of cyclin E–CDK2 activity and modulators of ubiquitin-dependent proteolysis are among the emerging drugs being considered for cancer therapy.

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PERSPECTIVES: SURFACE SCIENCE

How Minerals React with Water

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The interaction of aqueous solutions with mineral surfaces is one of the most important chemical reactions occurring in nature. Such reactions play a major role in dissolution, precipitation, and sorption processes (*1–3*), affecting the composition and quality of natural waters, the formation of soils, the removal of CO_2 from the atmosphere, the uptake and release of plant nutrients, the mobility of heavy metal contaminants, and the global cycling of chemical elements. They may also be responsible for the sequestration of water on Mars (*4*) and the formation of prebiotic molecules early in Earth's history (*5*). Interfacial reactions between solid surfaces and aqueous solution are also important in the preparation and performance of metal-on-metal oxide catalysts, metal corrosion and surface passivation, the cleaning of semiconductor surfaces, chemical sensing, and water treatment.

In addition to the presence of water and atmospheric gases, natural mineral surfaces are often coated with thin layers of precipitates, such as iron or manganese oxides, organic matter, and microbial biofilms (see the figure). This level of complexity is difficult to study at the atomic scale under reactive conditions. Nonetheless, rapid progress is being made because of the recent development of in situ surface-sensitive experimental methods, such as scanning probe microscopy (STM) (*1*), and x-ray spectroscopy (*1*) and scattering (*6*) methods that use extremely intense light from synchrotron radiation sources. Furthermore, computational studies (*7–9*) are beginning to provide realistic models of solid–aqueous solution interface reactions and structures that are consistent with experimental results.

Relatively simple mineral surfaces, such as periclase (MgO) (100) or corundum (α-Al_2O_3) (0001), are amenable to x-ray spectroscopic and scattering studies and high-level theoretical simulations. Synchrotron-based photoemission studies (*10, 11*) have shown that when water vapor first reacts with clean periclase or corundum surfaces, water molecules dissociate and react with a small concentration of defect sites at very low vapor pressures. Above a threshold pressure, water reacts with terrace sites, resulting in extensive surface hydroxylation. Recent theoretical simulations (*7–9*) are consistent with this interpretation.

The surface structure derived from these simulations is consistent with the structure of the hydrated α-Al_2O_3 (0001) surface recently determined with synchrotron-based crystal truncation rod diffraction (*12*). Heretofore, many surface and colloid chemists and geochemists assumed that hydrated mineral surfaces—particularly those of insulating materials such as corundum, which cannot be studied by STM—are adequately described as simple terminations of the bulk crystal structures. Eng *et al.* (*12*) showed that the upper atomic layers in the hydrated corundum surface are relaxed substantially relative to the bulk structure and the clean surface (*6*) and that the hydrated surface is oxygen- rather than Al-terminated, with each oxygen bonded to two Al atoms in the layer below.

This observation helps to explain the difference in reactivity between the clean and the hydrated alumina surface. The surface Al sites on the clean surface are strong Lewis acids. After hydroxylation, all surface sites are weak Lewis bases with lower reactivity to water but enhanced reactivity toward metals. This change may also help to explain the enhanced wettability of the hydrated alumina surface toward metals such as copper (*13*), which may alter the activity of alumina-supported Cu catalysts.

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