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CELL BIOLOGY: Balancing Life-or-Death Decisions

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effect. When the emission rate in the laser mode is much greater than that coupled to the residual leaky optical modes in the 2D slab, thresholdless operation (*7*) would be possible. Thus, the *Q* factor of the nanocavity is an important measure of the optimization of the desired emission process. Nanocavity *Q* factors have improved from hundreds in 1999–2000 (*8*) to ~50,000 in 2003 (*1*), ~600,000 in 2005 (*9*), and >1 million currently (*10*, *11*). Although *Q* factors of >1 million are not essential for thresholdless lasers, the realization of such ultrahigh-*Q* nanocavities is important to control the interaction between photonic and electronic systems.

Ongoing studies also aim to demonstrate that the carriers stored by the suppression of spontaneous emission can be used to induce emission coupled to the single-cavity mode instead of the residual leaky modes in a 2D slab (*6*). Quantum dots (QDs), which can confine carriers three-dimensionally, are the most promising light emitters to be introduced into nanocavities. This 3D carrier confinement allows nonradiative processes to be suppressed. In addition, the gain curve becomes sharp due to the delta-function–like density of states of QDs (*12*). Furthermore, QDs can reach absorption saturation easily due to their strong nonlinearity, and a high *Q* factor of the nanocavity can be maintained even during the initial stages of the excitation. However, the bottleneck blocking the demonstration of thresholdless operation arises because high-quality QDs can be obtained only by self-assembly methods; hence, the wavelengths and positions of the QDs in the nanocavity are random (see the figure). If the cavity mode is resonant with respect to the wavelength and position of the QD, the Purcell effect occurs (*2*, *13*), and the carriers stored by inhibiting spontaneous emission can be used mostly for emission coupled to the single-cavity mode, allowing thresholdless operation to occur. However, if the wavelengths and positions of QDs are not resonant with the cavity mode, the Purcell effect is suppressed and the emission rate of the cavity mode cannot be improved (*2*), leading to the consumption of excited carriers by emission coupled to the residual leaky modes. Thus, a clear demonstration of thresholdless operation remains to be achieved. Nevertheless, a recent paper (*4*) reported that the self-tuned QD gain effect is feasible, in which nearly thresholdless behavior might be obtained even in the off-resonant case. Although a detailed investigation of this effect is necessary, the report could be useful in addressing the matter of carrier concentration.

Major progress toward the realization of thresholdless nanolasers has clearly been achieved with 2D photonic crystal–based nanocavities and their fusion with QDs. However, to accomplish thresholdless laser operation, more needs to be done, including detailed investigations to clarify the interactions between the nanocavity and QDs in an off-resonant condition, and between individual QDs inside the nanocavity. There also needs to be progress in the development of 3D photonic crystals (*14*, *15*). The suppression of undesired spontaneous emission would be at least 10 to 100 times as great as that in a 2D photonic-crystal slab. Even if the QDs and the nanocavity mode were off-resonant, thresholdless operation would be expected because spontaneous emission coupled to residual leaky modes would be reduced to <0.06 to 0.6%. And finally, we must find an appropriate method of current injection (*16*) by which the *Q* factor of the nanocavity is not degraded. The future looks bright on all these fronts.

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CELL BIOLOGY

Balancing Life-or-Death Decisions

Jiri Bartek and Jiri Lukas

Phosphorylation of transcription factors is crucial to whether DNA damage in a cell results in cell death or repair and survival.

At the heart of the ability to self-replicate lies the cell's cycle machinery that orchestrates the flawless duplication of the genome and cell division. The major driving force of the cell cycle engine is the family of cyclin-dependent kinases (CDKs), enzymes that phosphorylate (add phosphate to) a number of cellular proteins. This modification fuels sequential transitions through the cell division cycle (*1*). Recent exciting discoveries show that CDKs may have yet another critical role in cell physiology—to coordinate cell cycle progression with timely responses to DNA-damaging insults that can threaten genomic integrity and cause devastating diseases such as cancer. The latest insight into this other role is published on page 294 of this issue by Huang and colleagues (*2*). These authors show that CDK-mediated phosphorylation of a transcription factor known as FOXO1 during S phase—the most vulnerable period of the cell cycle, when the 3 billion bases of human genomic DNA must be faithfully replicated—controls a cell's survival under genotoxic stress conditions.

In response to replication stress or DNA damage, cells activate a complex network of factors (*3*, *4*) that silence CDKs and thereby delay or arrest cell cycle progression (the so-called checkpoint pathways), promote DNA repair, or, in the case of irreparable damage, eliminate the potentially hazardous cell by induced cell death (apoptosis) (see the figure). The damage alert triggered by DNA lesions that activate these cellular responses is spread by two signaling modules of the checkpoint kinases ATM and ATR that activate the effector kinases Chk2 and Chk1, respectively (*3*, *4*). A key substrate of Chk1 and Chk2 is the Cdc25A phosphatase. Under normal physiological conditions, this enzyme strips the inhibitory phosphate molecule from CDK2, thereby activating it. CDK2 regulates the G_1-S transition and S-phase progression of the cell division cycle. After DNA damage or stalling of DNA replica-

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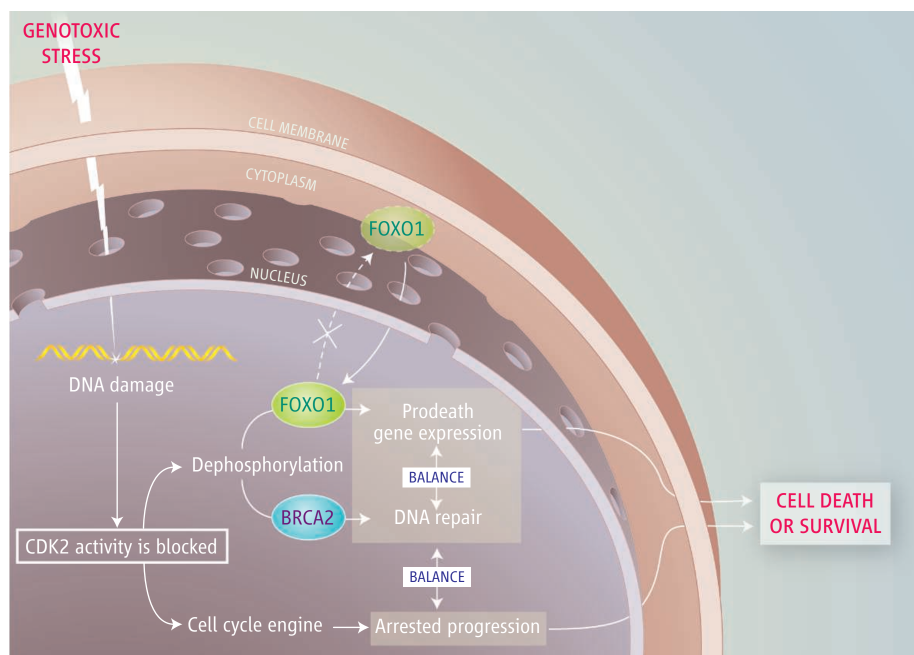

Cell fate decisions after DNA damage. In response to DNA lesions, CDK2 is inhibited, thereby withdrawing the CDK-mediated protection from unwanted death or DNA recombination. As a result, a cell may coordinately stall cell cycle progression and activate factors that allow cells to repair DNA by recombination (BRCA2) and survive, or trigger cell death (FOXO1). How the equilibrium between a productive repair (followed by a return into the cell cycle) and cell death is achieved remains unclear.

tion, Chk1/Chk2-mediated phosphorylation of Cdc25A triggers rapid degradation of the phosphatase by the proteasome (*4*). The resulting inhibition of CDK2 then plays a central role in DNA damage–activated cell cycle arrest (*4*) and DNA repair (*5*). However, it has been unknown whether CDK2 also influences cell survival, an issue elucidated in the new work by Huang *et al*.

In search of a possible link between CDK2 and regulation of cell death, Huang *et al*. identified FOXO1, the transcriptional activator of proapoptotic genes (*6*), as a substrate of CDK2. During unperturbed S phase, CDK2 phosphorylates FOXO1 on a serine residue (Ser^{249}) in a region that localizes the transcription factor to the nucleus. This modification sequesters FOXO1 in the cytoplasm, away from its nuclear target proapoptotic genes. When cells are exposed to insults that cause DNA damage, CDK2 becomes inhibited through the Cdc25A degradation pathway (*4*), resulting in dephosphorylation of FOXO1-Ser^{249}, subsequent nuclear localization of FOXO1, and activation of genes that promote cell death. When FOXO1 expression was down-regulated by small interfering RNA–mediated knockdown, or when a FOXO1 mutant that mimics its serine-phosphorylated form was expressed, cells exposed to DNA-damaging drugs or radiation were prevented from dying. In contrast, when CDK2 activity was neutralized by either a small-molecule inhibitor or the expression of a FOXO1 mutant that is not phosphorylated by CDK2, the nuclear localization of FOXO1 and cell death increased.

These elegant experiments and those on the role of CDK2-mediated regulation of DNA repair by homologous recombination (*5*) illustrate an emerging role for CDKs in orchestrating cell fate decisions in response to genotoxic stress. During unperturbed DNA replication, CDK-mediated phosphorylation of the transcription factors BRCA2 (*5*) and FOXO1 (*2*) renders the DNA recombination and cell death mechanisms, respectively, temporarily inactive, yet ready to step in when cells encounter DNA damage and cell cycle progression is blocked through the CDK-silencing checkpoint cascades. In addition, other aspects of genome integrity maintenance, such as processing the ends of broken DNA (*7*) or recruitment and assembly of additional factors to sites of DNA damage (*8*), appear to be controlled by analogous CDK-mediated phosphorylations. Given the many pathways that respond to DNA damage, the list of CDK substrates involved in processes that coordinate cell cycle progression with the emergency responses is likely to grow.

As Huang *et al*. point out, their work also has important implications for understanding cancer pathogenesis and disease management. In cancer, CDK2 activity is commonly deregulated and the DNA damage response machinery that was recently identified as a barrier against oncogene-driven progression of early human lesions to malignancy (*9*, *10*) is often defective (*3*). Both unscheduled CDK2 activity and malfunction of the genome maintenance mechanisms may lead to inefficient induction of cell death, and hence to aberrantly enhanced resistance to widely used DNA-damaging treatments including ionizing radiation and chemotherapy.

These new discoveries raise a host of questions. What ensures that FOXO1-mediated apoptosis (*2*) or BRCA2-mediated genome repair (*5*) in response to DNA breaks occur during the S phase, but not in the G_1 phase, of the cell cycle? For BRCA2, we know that the high CDK activity needed to allow processing of DNA breaks is unavailable in the G_1 phase (*7*). Similarly, CDKs could also restrict FOXO1-induced cell death because phosphorylation of an additional target(s) in the pathway is required for efficient expression or accumulation of proapoptotic effectors. Also, given that both BRCA2-mediated DNA repair and cell death pathways are activated upon silencing of CDK activity in response to DNA damage, what determines the duration and final outcome of such processes? Perhaps a longer persistence of CDK2-mediated phosphorylations, such as FOXO1-Ser^{249} (*2*), and the requirement for transcription and subsequent accumulation to threshold levels of the FOXO1-regulated factors, give a cell the chance to repair the damage and resume proliferation. Does transient activation of a prosurvival transcription program by the DNA damage machinery itself, such as the ATM–NEMO–nuclear factor κB cascade (*11*), open a transient window of opportunity for a successful repair before cell death prevails? Understanding how cells balance life-and-death decisions may help us to ultimately save patients' lives.

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