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The yin and the yang of p27^{Kip1} as a target for cancer therapy

B.Eymin and E. Brambilla

Schematically, human tumors arise because tumor cells escape from extracellular signals that physiologically monitor cellular proliferation as well as cell death and acquire the property to grow continuously. During tumorigenesis, many proteins that normally control the proper timing of cell growth such as the cyclins or prevent the occurrence of inappropriate apoptosis are abnormally expressed or activated and act as typical oncogenes leading to hyperproliferation and/or protecting tumor cells from death. In contrast, proteins that normally prevent for example damaged cells to progress into the next phase of the cell cycle or act as apoptosis inducers if the damage can not be repaired are frequently inactivated in tumor cells and act as tumor suppressor genes. Therefore, loss of tumor suppressor genes associated with abnormal hyperactivity of oncogenes classically contribute to human carcinogenesis. However, affecting a clear-cut function of tumor suppressor or oncogene remains a subject of debate for certain proteins. p27^{Kip1} is a member of the cyclin dependent kinase inhibitory proteins which also include p21^{WAF1}, the target gene of p53, p16^{INK4a}, a member of the retinoblastoma (Rb) pathway and p57^{Kip2}. With p16^{INK4a}, it plays a major role in counteracting the activity of cyclins D₁ and E on Rb phosphorylation and subsequent G₁-S transition. Thus, it coordinates the activation of cyclin E-cdk2 with accumulation of cyclin D-cdk4 and initiates the timely exit of cells from the cell cycle in response to antimitogenic signals. Beside its classical anti-proliferative function, p27^{Kip1} can also promote or inhibit apoptosis depending on the context (1,2). Based on these data, p27^{Kip1} presents most of the classical features of a tumor suppressive protein that might be loss in proliferative tumor cells.

Unlike most of the tumor suppressor genes which loss of function responds to the classical "two-hit hypothesis" of tumor suppression (Knudson law), p27^{Kip1} gene is not deleted (neither loss of heterozygosity nor homozygous deletion) not mutant, and does not suffer aberrant methylation of its 5'-end in tumors. Rather, in mouse models, p27^{Kip1} was shown to be a dosage dependent tumor suppressor since loss of a single allele of p27^{Kip1} increases the frequency and decreases the latency of tumors to a level intermediate to that seen in wild-type and null counterparts (3).

In human tumors, a direct correlation between p27^{Kip1} protein levels and survival chances was first noted in colon cancer and later in cancers of the breast, prostate, bladder, ovary, lung and other tissues (for review, see 4). The evidence that reduced p27^{Kip1} may contribute to tumor development by either increasing the proliferation of cells or decreasing their apoptosis might explain why the loss of p27^{Kip1} is a common marker among many different tumor types and suggest that p27^{Kip1} might be a valuable target for both stratifying patient risk and, perhaps, selecting treatment. However, observation that some human tumors exhibit high levels of p27^{Kip1} makes this scheme more complex. For example, in aggressive small cell lung cancer, p27^{Kip1} overexpression has been suggested to protect cells from apoptosis in unfavorable microenvironments (5). In addition, p27^{Kip1} might affect the efficacy of chemotherapies as these treatments works better in proliferating rather than in growth-arrested cells. Therefore, we need to keep in mind that modulating p27^{Kip1} levels can have unforeseen consequences on therapy depending on the cell type and the contextual clues.

In this issue, Ishii and colleagues (6) have studied the consequences of p27^{Kip1} overexpression or downregulation in human lung adenocarcinoma. They first show that overexpression of p27^{Kip1} inhibits cell growth and rescues cells from death instead of inducing apoptosis. More interestingly, using siRNA technology, they demonstrate that neutralization of endogenous p27^{Kip1} induces cell death of several non small cell lung cancer cell lines without affecting their cell cycle status. Finally, after analysis of p27^{Kip1} subcellular localization and phosphorylation, they describe the predominant cytoplasmic accumulation of endogenous

p27^{Kip1} in these tumor cells which might preclude it from regulating the G₁/S transition. p27^{Kip1} activity appears to be directly targeted by its mislocalization to the cytoplasm in colon or ovarian tumors (7,8) and cytoplasmic p27^{Kip1} seems to correlate with poor-long term survival and tumor grades in breast carcinoma (9). Mislocalization effectively inactivates p27^{Kip1} inhibitory activity, as cytoplasmic p27^{Kip1} is partitioned from its nuclear cyclin-cdk targets. However, as suggested by Ishii and colleagues, such cytoplasmic localization of p27^{Kip1} could also contribute to its anti-apoptotic functions. Therefore, before considering therapies, we need to predict how cells in a particular tumor will respond to accumulation or neutralization of p27^{Kip1}. In this context, the study of Ishii and co-workers suggests that targeting p27^{Kip1} in non small cell lung cancer could inhibit their growth by reducing cell viability. In contrast, in other tumor types, it will be the restoration of p27^{Kip1} that will prevent tumor growth, either by inhibiting cellular proliferation or inducing apoptosis. So, depending on the cancer type, the goal of therapy targeting p27^{Kip1} will tend to either neutralize or reintroduce it. It is the reason why comprehensive understanding of p27^{Kip1} biology would facilitate development of such therapeutic responses in human cancer. So, it would be too simplistic to ascribe p27^{Kip1} only as a tumor suppressive protein since its anti-apoptotic function might also predict an "oncogenic" role. As a typical example of this "gain of function" are the highly aggressive small cell lung cancer which carry elevated levels of nuclear p27^{Kip1}. Obviously, more need to be done to decipher the real contribution of p27^{Kip1} in human lung tumor growth. In conclusion, it is now well established that the biological effects of numerous proteins might be quite different, sometimes even opposite, depending on the cellular model, the context as well as their subcellular localization. Therefore, before designing general therapies against cancer, we have to study very carefully the specific proteins involved in each carcinogenetic process as well as to investigate the molecular mechanisms by which the loss or hyperactivity of such proteins contribute to the carcinogenesis. Finally, we have to think about the fact that modulating the level of proteins that controls essential processes such as cellular proliferation and apoptosis might interfere with the response of tumor cells to chemotherapeutic treatments as well as to have unpredicted consequences.

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