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

Béatrice Eymin, Elisabeth Brambilla

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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 unappropriate 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 D_1 and E on Rb phosphorylation and subsequent G_1-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 heterozygozity 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 G_1/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 agressive 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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