Deregulation of cyclin-dependent kinase activities in human cancer has been linked to the inability of tumor cells to respond appropriately to intra- and extracellular proliferation control mechanisms. Numerous studies have appeared over the past 15 years describing both inactivation of cyclin-dependent kinase inhibitory proteins and upregulation of cyclin expression [1]. Downstream of cyclin-dependent kinases in G1, the retinoblastoma protein (pRb) has been described as a critical regulator of the progression through the G1 phase of the cell cycle and into S-phase. Cdk4, Cdk6 and Cdk2 have all been implicated in inducing pRb phosphorylation and progression through S-phase. Yet, despite the large number of in vitro studies conducted to prove this point, in vivo genetic inactivation studies are questioning the critical role played by these cyclin-dependent kinases [2–4]. Constitutive or inducible inactivation of Cdk2 in mouse has failed to generate a block in cell proliferation without any effect on mouse viability, suggesting the possibility that the function of Cdk2 is replaced by a related Cdk (possibly Cdk1?) or that alternative means for pRb inactivation exist in these cells. Similar findings have shown a redundant role for Cdk4 and Cdk6 and for three D-cyclins. Yet, despite these findings, studies of Cdk function upregulation in tumors continue to appear in the literature, supporting the role played by these protein complexes in cancer. Work by Dr. Hideki Ishihara’s laboratory in Kobe (Japan) now shows an upregulation of Cdk2 protein kinase activity in gastrointestinal tumors, compared to normal tissue adjacent to the tumor analyzed. The study, although limited to 37 patients, is intriguing; the authors have developed a very simple method that could be easily implemented as a routine test in clinical pathology laboratories. These laboratories are best suited to perform these analyses, since execution of functional protein-based tests requires appropriate handling of fresh tissue to prevent protein degradation and inactivation. Once fully validated, the test developed by the Ishihara group might allow larger studies to be performed. These studies could be extended to larger patient cohorts with the aim of establishing whether deregulated Cdk2 activity correlates with tumor progression and patient prognosis, as well as with other molecular signatures.

References


E-mail address: giulio.draetta@merck.com.