Tumor suppressingfunctions of p16INK4a-A review

Abstrak

DNA damage can have particularly severe carcinogenic influence if it incapacitates the cellular machinery normally protecting the cell from the effects of genomic damage. The protective functions involve not only DNA repair and apoptosis (programmed cell death), but also regulation of the cell cycle and proliferation. Therefore, carcinogenesis can be promoted by inactivating or altering key regulatory proteins like p16INK4a, which has the capability to arrest the cell cycle in the G1 phase and prevent inappropriate proliferation. Functional cyclin-dependent kinase (Cdk) inhibitor p16INK4a binds to Cdk-4 and Cdk-6, thereby preventing the Cdk-cyclin complexes from promoting phosphorylation of pRb and releasing the transcription factor E2F needed for the cell cycle to proceed to the S phase. Arrest in G1 accounts for a minority of arresting cells after DNA damage, the majority of arrests taking place in G2 without recognized p16INK4a contribution. However, inactivating alterations of p16INK4a are common in cancers, possibly because of additional functions of p16INK4a in senescence and inhibition of the spreading and migration of cancer cells. Since oncogenic initiation is insufficient for growing significant tumors without spreading and angiogenesis, this could partly explain why inactivated p16INK4a is frequently exhibited in clinical tumors in spite of apparently less exclusive role in cell cycle arrest. On the other hand, multiple oncogenic events are usually necessary to develop cancer, and generally both pRb and p53 pathways are impaired in tumors. This suggests that growth regulation in G1 and therefore also its key molecular components including p16INK4a are important in carcinogenesis.