CDK9 as a novel therapeutic target and prognostic marker in cancer

The last decades have brought immense progress in cancer therapy and patient care. Unfortunately, current systemic therapies are not devoid of limitations and prompt the search for novel therapeutic targets and prognostic markers. As a result, the FDA and EMA recently approved cyclin-dependent kinase 4/6 (CDK) inhibitors for treating advanced breast cancer. One of the most promising therapeutic targets is CDK9, which is considered a central hub of transcription regulation. Its overexpression increases the levels of anti-apoptotic proteins, such as Bcl-2 and Mcl-1, and decreases the activity of p53, thereby facilitating carcinogenesis. This project aims to determine the prognostic significance of CDK9 in human cancers, define the applicability of CDK9 inhibitors for clinical use, and identify patients who may benefit most from therapy. Analysis of CDK9 expression in bladder cancer (BLCA) revealed that high CDK9 tumors tended to be lower grade, later stage, and non-muscle invasive compared to low CDK9 tumors. In addition, high CDK9 expression predicted longer patient survival in both the TMA and The Cancer Genome Atlas cohorts, which is in contrast to reports from other cancers. In our cohort, high p53 expression predicted shorter survival in non-muscle-invasive bladder cancer. Tumors with high p53 also had high levels of CDK9, but we did not find a linear correlation between p53 and CDK9 expression. The complex relationship between both proteins should be taken into account when conducting preclinical studies in BLCA. Due to the low efficacy in monotherapy, the utility of CDK9 inhibitors has not been fully determined. Therefore, further studies should consider the use of more selective CDK9 inhibitors, CDK9 degraders, and their incorporation into current therapeutic regimens as adjunctive agents instead of monotherapy. Considering the synergistic effects between CDK9 inhibitors and sorafenib, clinical trials in HCC seem to be only a matter of time. Literature data suggest that efforts should be focused on patients with p53 mutation, as this group can achieve the greatest clinical benefit. Despite recent progress, the hope of finding drugs that overcome resistance to therapy may be premature. Therefore, all theoretical concepts should be proven in future trials.