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Editorial Open Access

PI3K Inhibitors: Novel Molecular-Targeted Drug Candidates for Cancer Therapy

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Editorial

Phosphatidylinositol 3-kinases (PI3Ks) are a class of lipid kinases that phosphorylate phosphatidylinositol 4,5-bisphosphate (PIP2) at the 3-OH of the inositol ring to generate phosphatidylinositol 3,4,5-trisphosphate (PIP3) which activates Akt and its downstream effectors like mTOR, and therefore play important roles in cell growth, etc [1-3]. The phosphatase and tensin homolog deleted in chromosome ten (PTEN), acts as the catalytic antagonist of PI3K by dephosphorylating PIP3 to PIP2. Because gain-of-function mutations of PIK3CA which encodes PI3Kα, as well as loss-of-function mutations of PTEN, were frequently found in human cancers, PI3K became a potential drug target for cancer therapy. Correspondingly, development of PI3K inhibitors has led to a race among pharmaceutical companies: until now, over 20 compounds targeting PI3K have been in clinical evaluation for cancer therapy.

Akt, the downstream effector of PI3K, is well known to be closely involved in cell survival, however, targeting PI3K seems not necessarily leads to apoptosis [4]. Accumulating preclinical data have shown that G1 arrest is the main mechanism contributing to the antitumor efficacy of PI3K inhibitors [4], while some of them were reported to induce apoptosis in a subset panel of cancer cells particularly those with HER2 amplification and/or PIK3CA mutation [5]. Anti-angiogenesis and normalization of the vasculature in tumor may also contribute to the in vivo antitumor effect [6,7].

PI3Ks include 4 isoforms: α, β, δ and γ. Discovery of PI3Kα-specific inhibitors was originally pursued for cancer therapy based on the understanding that only PI3Kα gene (PIK3CA) mutations and amplification were observed in human cancers, and that further inhibition of other isoforms might cause side effects. However, most PI3K inhibitors in clinical evaluation are pan-PI3K inhibitors (without obvious isoform selectivity) [8], and they exhibit no obvious toxicity [9]. Moreover, accumulating reports have indicated that besides PI3Kα, other PI3K isoforms are also involved in tumorigenesis [3,10], suggesting that a pan-PI3K inhibitor might offer enhanced therapeutic efficacy compared with PI3Kα-specific inhibitor, which has been demonstrated in preclinical experiments [11].

Predictive biomarker identification has provided important information for patient selection in the future: PIK3CA mutation, HER2 amplification and p-Akt expression have been reported as potential predictive biomarkers [12,13]. On the other hand, p-Akt and p-S6 may be feasible pharmacodynamic biomarkers for monitoring treatment with PI3K inhibitors [14].

Since PI3K inhibitors mainly exhibit cytostatic activity, combination with cytotoxic therapy approaches might be a better strategy for cancer therapy. Some PI3K inhibitors have indicated synergic efficacy with radiotherapy or conventional chemotherapy [9,15,16]. Increased antiumor effects were also reported for combination with other molecular-targeted antitumor drugs which target MEK, mTOR, etc [17].

As an exciting information, some phase I data of the most advanced PI3K inhibitors such as GDC-0941 have been available, which indicate that patients generally tolerate these drug candidates, demonstrating their safety. As the remaining clinical trials go forward [16], the first PI3K inhibitor is expected to appear in clinic in the near future.

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