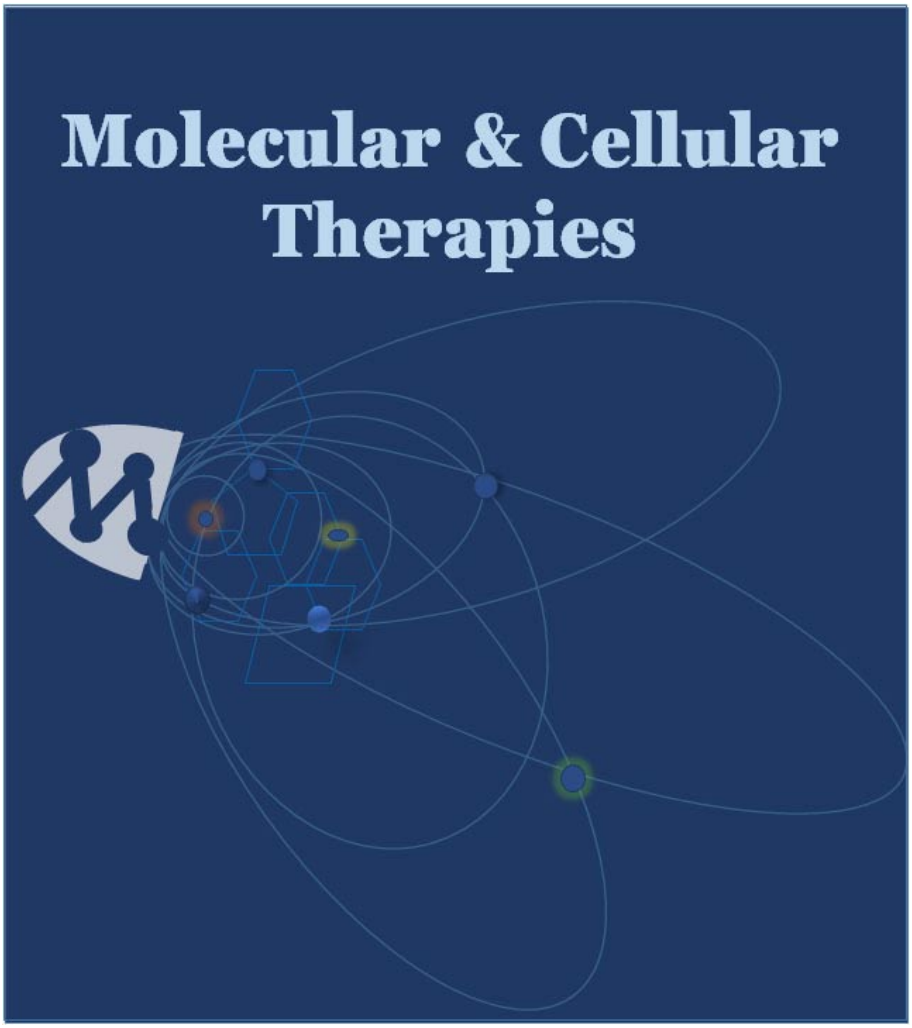

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Spotlights

Magic power of phosphoinositide 3-kinase inhibitors

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Summary

Phosphoinositide 3-kinases (PI3K) play critical roles in the maintenance of cell biological functions and are suggested as a therapeutic target for drug discovery and development. PI3K inhibitors has the magic power to prevent the development of pathological changes and cure the diseases, while such magic powers can be faded by the large profile of their toxicity and side-effects. A number of strategies can prevent, reduce, or decline PI3K inhibitor-associated toxicities, e.g. to make the inhibitors targeting the core molecules more precisely, select the optimal approach of drug delivery, bind the "recognizing" pullets with PI3K inhibitors to target-specific cells, or gene editing. We spotlight that PI3K definitely is an important therapeutic targets for cancer, inflammation, or organ dysfunction and injury, while to catch and hold such magic power of PI3K inhibitors is still the challenge to be faced and solved.

Phosphoinositide 3-kinases (PI3K), also named Phosphatidylinositol-4,5-bisphosphate 3-kinases, phosphatidylinositide 3-kinases, or phosphatidylinositol-3-kinases, are one of the most important enzyme families in multiple aspects. Fruman et al recently overviewed the development of PI3K pathway-targeted therapies for cancer, including PI3K biological functions, druggability, efficacy and toxicity of inhibitors, and especially addressed the roles of class I PI3Ks in the regulation of cellular metabolism and in immune system functions [1]. According to primary structures, regulatory functions, and lipid substrate specificity, PI3K has four classes I-IV, of which there are a number of subtypes in each class with different biological function. For example, class II PI3K has the subtypes of C2α, C2β, or C2γ, of which PI3K-C2α is involved in the maintenance of platelet function by regulating α-granules and membrane structure,amounts of PI3P, or re-localization of membrane skeleton proteins. Platelets without PI3K-C2α fail toform filopodiaor thrombus formation. PI3K-C2β contributes to cell metabolism of glucose and insulin sensitivity by regulating endosomal trafficking of activated insulin receptors in class I PI3K-dependent Akt signaling. PI3K-C2γis also involved in insulin sensitivity by binding with Rab5-GTP and recruiting to Rab5-positive early endosomes through selective reduction of Akt2 activation. It seems that each of PI3K subtypes can be a potential drug target for special therapy and the inhibitors of PI3K family has the magic power to prevent the development of pathological changes and cure the diseases.

Such magic powers of PI3K inhibitors are faded by the large profile of their toxicity and side-effects. deWeerdt et al recently investigated the safety and toxicity profiles of idelalisib with Ibrutinib on basis of data from clinical trial reports [2]. Thefatal and serious toxicities including liver toxicity, diarrhea and colitis, pneumonitis and intestinal perforationoccurred during idelalisib treatment. It is understandable that PI3K inhibitors have a large number of toxicities, since PI3K has a long list of biological functions too, e.g. cell growth, proliferation, differentiation, motility, survival, intracellular trafficking, metabolism, and immune response. It has been discussed for the long time how to develop more efficacy and less toxicity of PI3K inhibitors for cancer and inflammation. One strategy should be considered to make the inhibitors targeting the core molecules more precisely or to approach the core molecule in subtypes of PI3K classes. DNA-encoded chemical libraries (DELs) is an important approach with billions of compounds to screen novel ligands and inhibitorsheading to more precise biological targets. Shi et al recently presented a novel "ligate-cross-link-purify" strategy to select DELs against unmodified and non-immobilized protein targets [3]. Such outstanding strategy breakthrough the barrier where DELs were used to often select against purified and immobilized proteins and can uncover binders with moderate and weak affinities. It would be an alternative to screen candidate drugs more precisely targeting the core moleculeof PI3K to prevent from the largetoxicity profiles of new categories of PI3K inhibitors

Another strategy is to find the optimal administration

of PI3K inhibitor delivery which can reduce the amount of drug used for therapy. Massacesi et al overviewed thestrategies to maximize the efficacy of PI3K inhibitors in clinical trials and clearly pointed out that different approaches of drugs offered various efficacies, dependent upon cancer types [4]. From our experience, we found that the dose of PI3K inhibitors administered intratracheally was about 50-60 folds less than that given orally to gain the same efficacy, when PI3K inhibitors were used to prevent and treat the inflammation-induced acute lung injuries [5].This was an initial study to define the therapeutic windows of PI3K inhibitors between local and systemic drug deliveries in non-cancer pathology. Lung diseases are the optimal model to investigate the therapeutic windows of drug doses, since drugs can approach the pathology fastest and most directly by intranasal or intratracheal instillation or inhalation. We also evidenced that PI3K could play critical roles in the development of protease-induced acute and chronic lung inflammation, remodeling, and emphysema in animals, which can be prevented by the intratracheal instillation of PI3K inhibitors. The systemic doses which had significant efficacy could induce severe illness and death of animals after the intravenous injection of PI3K inhibitors.

More issues should be considered to approach the magic power of PI3K inhibitors. It would be the ideal approach of PI3K inhibitors to specifically identify and target the cancer cells or compromised cells by the binding with the “recognizing” pullets which can direct PI3K inhibitors to target cells, rather than normal cells. PI3K inhibitors only can transmembrane into the target cells after the pullets find and bind with the target cells. Gene editing provide the imaging space to precisely regulate PI3K genes. For example, the clustered regularly interspaced short palindromic repeats (CRISPR) can edit the specific gene sequences of PI3K genes to reach the inhibitory effects of PI3K subtypes by down-regulating PI3K genes. It is a challenge to define the specific repeated sequences of one PI3K gene among 14 genes, and confirm the protein0level effects of genetic down-regulation, since multiple genes can be involved in the transcription and synthesis of one PI3K protein. It is also the challenge to find PI3K-activation-specific and measurable biomarkers for clinical application, since the measurement of fluid biomarkers specific to PI3K activation and inhibitory effects, especially PI3K subtypes, in patients is hardly performed in clinic. We conclude that PI3K definitely is an important therapeutic targets for cancer, inflammation, or organ dysfunction and injury, while to catch and hold such magic power of PI3K inhibitors is still the challenge we have to face and solve.

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