Drug Discovery by Targeting Mutant KRAS

Cancer is the second leading cause of death globally and is estimated to account for 9.6 million deaths in 2018. In other words, about 1 in 6 deaths is due to cancer. These numbers are expected to rise to over 15 million by the year 2035. RAS proteins, including KRAS, NRAS and HRAS, play an important role in cell growth, differentiation, proliferation and survival by regulating diverse cellular pathways. KRAS is known as a human oncogene for over 30 years, and is the most frequently mutated class of Ras family in all human cancers (21.6%), especially with the highest prevalence in pancreatic adenocarcinomas (90%), colorectal cancers (45%) and lung cancers (35%). Therefore, KRAS represents as an intriguing and promising cancer target, and research efforts towards discoveries of new approaches to targeting mutant KRAS are imperative to offer exciting opportunities in pursuit of developing better therapeutics that can benefit cancer patients. Currently, AMG 510, a potent and selective KRAS G12C covalent small molecule inhibitor developed by Amgen, shows good tumor response in a phase I clinic trial for non-small cell lung cancer and colorectal cancer. And a KRAS siRNA molecule also entered into Phase II clinical trials of pancreatic cancer.

This issue contains a diverse collection of reviews aiming to provide the intensive quest in developing effective approaches to combat various KRAS-mutant-driven cancers, point out the difficulties, and point the direction for future research. Cheng et al. provide an overview of treatment of KRAS mutant cancers including directly targeting oncogenic KRAS protein by a virtual screening approach to discover novel KRAS inhibitors [1]. Liu presents an overview of the emerging new therapeutic approaches for inhibiting KRAS signaling and blocking KRAS functions including nano-therapeutic approaches, inhibition of KRAS mutation-mediated metabolic pathway, and inhibition of cell cycle regulation. Since KRAS proteins must be associated to the plasma membrane for their function, targeting KRAS plasma membrane localization represents a logical and potentially tractable therapeutic approach [2]. Ye et al. highlight the recent advances in the development of KRAS plasma membrane localization inhibitors including natural product-based inhibitors achieved from high throughput screening, fragment-based drug design, virtual screening, and drug repurposing as well as hit-to-lead optimizations. Inhibition of upstream cell surface receptors (e.g. EGFR inhibitors) results very brief effects due to the rapid development of drug resistance or tumor recurrence, while inhibition of KRAS downstream effectors results in limited clinical efficacy, thereby the combination therapy is essential for the treatment KRAS mutated cancers [3]. He et al. present the recent advance in applications of drug combinatorial therapies for treatment of KRAS mutated lung cancers. Since RNA interference (RNAi) technologies can efficiently eliminate the expression of specific genes, using RNAi molecule to selectively target KRAS and KRAS's synthetic lethal interactions are an effective individualized targeted drug therapy to KRAS mutant cancers [4]. Liu et al. highlight the current status, future perspective and associated challenges in the application of the RNA interference technologies for KRAS. Cancer immunotherapy is a targeted and personalized approach employing either adoptive T cell transfer, vaccines, antibodies, CAR-T cells, immune checkpoint inhibitors or other immunological components to increase therapeutic efficacy while reducing unwanted side effects commonly associated with conventional cancer therapy [5]. In and colleagues focuse on current immunotherapeutic developments and advances in both pre-clinical and clinical studies directly or indirectly targeting KRAS via its downstream signal transduction machinery [6]. Pancreatic cancer is a highly malignant tumor with poor prognosis and high recurrence rate and death rate. Since KRAS mutations have been identified in 60% to 90% of pancreatic cancer, Hao et al. specifically highlight the occurrence and treatment of pancreatic cancer harboring KRAS mutations [7].

As the Guest Editor, I would like to thank all the authors for their tremendous effort, dedication, and excellent contribution to this special issue of Current Topics in Medicinal Chemistry. I hope that this issue will serve as a key reference work for medicinal chemists, chemical biologists, cancer biologists and other research investigators engaged in or interested in drug discovery by targeting mutant KRAS.

REFERENCES


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