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A Review of KRAS Inhibitors and Potential Improvement in The Future

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Abstract. Kirsten rat sarcoma viral (KRAS) oncogene is one of the most common mutant genes in tumors, especially in non-small cell lung cancer, colorectal cancer, and pancreatic cancer. In recent years, great success was achieved in targeting KRAS for the treatment of tumors. So far, two drugs, sotorasib and adagrasib, have gotten through the accelerated approval by the FDA. Even so, current treatments are still far from satisfaction due to the inevitable acquired drug resistance and the diversity of mutant isoforms. Various approaches are being investigated to address these issues, including the combination of multiple medications and the development of drugs with more targets. Overall, targeting KRAS is a promising and effective strategy for the treatment of cancer. For this reason, the article aims at introducing several representative KRAS-targeting drugs and exhibiting the latest research progress. Discussions about the acquired resistance and the potential solutions are also included, hoping to provide inspiration for the development and improvement of new drugs.

Keywords: tumor; KRAS inhibitor; KRASi resistance; small interfering RNA; PanRAS inhibitor.

1. Introduction

KRAS mutations account for 85% of cancers induced by RAS [1]. The most frequent mutation in KRAS gene is in the codon encoding glycine residue 12 (G12). The main G12 mutations are G12C, G12D and G12V. In the past, KRAS was hardly considered as a “druggable” target due to the fact it lacks pockets large enough to bind small molecules. The critical role of KRAS in normal cell cycle also makes it difficult to target the upstream and downstream signal pathways of KRAS as it would have lots of side effects. Approval of KRASG12C inhibitors sotorasib and adagrasib has shattered this perception. The success of these two drugs has also spurred the development of other drugs targeting KRAS. Several new drugs have also entered the clinical trial stage. Nevertheless, existing KRAS inhibitors (KRASi) are challenged by the fact that oncology patients inevitably gain KRASi resistance. Besides, most drugs are aimed at KRASG12C. There is still a great research gap in other KRAS mutation isoforms as they still occupy a considerable proportion in RAS induced tumors. Fortunately, several molecules targeting other mutations are under research and they have the potential to address the problem of the versatility of KRAS inhibitors. There are also studies working on the application of KRASi to other diseases. Herein, the author provide a review of several drugs targeting KRAS including their mechanism and efficacy, as well as discuss the inhibitor resistance and its solution.

2. KRAS mechanism

The main corresponding protein of KRAS after transcription and translation is a GTPase contains 188 amino acids. The molecular weight is about 21.6kDa. KRAS protein can be transitioned between inactivated and activated states. It is inactive when it binds to guanine nucleoside diphosphate (GDP) and is activated when it binds to guanine nucleoside triphosphate (GTP). The KRAS protein remains in inactivated state in most cells. The binding of KRAS to GTP or GDP is very strong, with an affinity of picomolar range. When KRAS protein is in active state, it can activate multiple downstream signaling pathways, such as RAF-MEK-ERK and PI3K-AKT pathways. These signaling pathways play an important role in promoting cell proliferation and survival. The transition of KRAS protein is regulated by two classes of cytokines. Guanine nucleotide exchange factors (GEF) including son

of sevenless homolog 1 (SOS1) protein can promote the activation of KRAS protein. GTPase-activating proteins (GAPS) can lead to the hydrolysis of GTP bound to KRAS protein into GDP ,which terminates the active state. Most KRAS mutations interferes with the hydrolysis process of GTP, resulting in long-term activation of KRAS protein and excessive cell proliferation. Additionally, KRAS transforms the phenotype of carcinoma-associated fibroblasts (CAFs) into lipid-laden CAFs, which promotes the production of vascular endothelial growth factor A (VEGFA) and stimulates angiogenesis [2]. Overall, available researches indicate KRAS mutations are critical to the development of cancer cells in many ways.

3. Marketed KRAS Drugs

3.1. Sotorasib (AMG-510)

Sotorasib (AMG-510) is an inhibitor that can bind specifically to KRASG12C. The binding is covalent and irreversible. At the molecular level, sotorasib binds to the allosteric pocket through its acrylamide structure. This binding can reduce the affinity between GTP and KRAS, prevent GEF from catalyzing GTP to replace GDP, and lock KRASG12C in an inactive state. In the Phase II CodeBreaK 100 study, the objective response rate of receiving a dose of 960 mg AMG-510 once daily was 37.1% [3]. It also demonstrated that the median duration of response was 11.1 months [3]. The FDA approved sotorasib in 2021 for the treatment of non-small cell lung cancer (NSCLC) with accelerated approval based on the Phase I/II clinical trial results. After the marketing of sotorasib, a larger phase III clinical trial compared the effects of sotorasib and docetaxel for the treatment of NSCLC. The research demonstrated that median progression-free survival with sotorasib improved by about one month compared with docetaxel, and the tolerability of sotorasib is higher as well [4]. Common adverse reactions observed in clinical studies include diarrhea, elevated alanine aminotransferase, and aspartate aminotransferase [3, 4].

Sotorasib is currently only approved for NSCLC. Since KRAS protein mediates a variety of signaling pathways, sotorasib is also promising for treating other diseases. Fraissenon et al. reported 2 cases in which taking sotorasib can significantly relieve arteriovenous malformations [5]. This implies that the therapy of vascular malformations may benefit greatly from sotorasib as well. In parallel, sotorasib is being researched and may be utilized to treat various KRASG12C-related cancers, such as colorectal cancer (CRC).

3.2. Adagrasib (MRTX849)

Adagrasib (MRTX849) is another KRASG12C covalent inhibitor with high selectivity. Its binding mechanism is similar to that of sotorasib. Comparatively, the drug half-life of adagrasib is longer. A median response time of 8.5 months and a median response rate of 42.2% were obtained when adagrasib 600 mg was taken twice daily in the Phase II study [6]. In December 2022, the FDA authorized adagrasib as a targeted therapeutic option for patients with KRASG12C mutations who have progressed or metastatic NSCLC. The most frequently occurring adverse reactions during adagrasib treatments are diarrhea, nausea, headache, and fatigue [6].

Another clinic trial demonstrated the combination of adagrasib and cetuximab was effective in the treatment of CRC. The ORR in the combination group was 46%, and the median DOR was 6.9 months [7]. Adagrasib was given accelerated approval by the FDA in June 2024 for a new indication, in conjunction with cetuximab, to treat patients with CRC who have KRASG12C mutations.

4. Drugs Under Study

4.1. Divarsib (GDC-6036)

After the approval of adagrasib and sotorasib, a number of new KRASG12C covalent inhibitors with comparable mechanisms have entered the clinical trial stage. Divarasib (GDC-6036) is one of the

promising candidates with great efficacy and selectivity. Results from the Phase I clinical trial showed that divarsib achieved response rates of 53.4% and 29.1% in NSCLC and CRC patients, respectively [8]. It demonstrated the potential for divarsib to outperform the two approved drugs in terms of efficiency and selectivity. In addition, the research indicated divarsib had good security, as dose reduction and discontinuation events accounted for less than 20% of the total, better than sotorasib and adagrasib [8]. More clinical trials, including blinded tests, are needed to support the efficacy of divarsib. Further investigations into divarsib combination therapy are also likely to provide new solutions against different kinds of KRASG12C-induced cancer.

4.2. MRTX0902

In addition to binding KRASG12C protein directly, targeting the upstream and downstream pathways of KRAS protein is also likely to alleviate tumor progression. As the main guanine nucleotide exchange factor, SOS1 directly regulates the activation state of KRAS protein and has become a popular target. Some molecules can disrupt KRASG12C protein-protein interactions (PPI) and reduce activated KRAS protein. MRTX0902 is a SOS1:KKRASG12C PPI inhibitor and was proved to be effective in the tumor mouse xenograft model [9]. MRTX0902 has entered the clinic trial stage. It is anticipated that such PPI inhibitors will enhance KRASG12C inhibitors in reducing aberrant activation of KRASG12C proteins.

4.3. MRTX1133

KRASG12D mutations account for the largest proportion of CRC. Nevertheless, the development of drugs targeting KRASG12D is lagging behind that of KRASG12C. Currently, the FDA has approved no medication that targets KRASG12D. Meanwhile, another concern is that long-term, irreversible binding may lead to unknown toxicity that is difficult to detect in shorter clinical trials. As a reversible non-covalent KRASG12D inhibitor, MRTX1133 has the potential to solve problems above. The study proved that MRTX1133 considerably (>30%) regressed tumors and had a high affinity for KRASG12D [10]. The advantage of MRTX1133 is that it also has an inhibitory effect on activated KRASG12D. MRTX1133 suggests that non-covalent binding of KRAS protein is also feasible for new drugs.

4.4. PanRAS inhibitors

The presence of multiple mutant subtypes of KRAS makes it difficult to meet the actual needs through inhibitors targeting a single subtype. For this reason, there is a demand of PanRAS inhibitors which are able to prevent the activation of various types of mutant KRAS. The main challenge with PanRAS inhibitors stems from the risk of toxicity due to non-specific binding. RMC-6236 is a promising PanRAS inhibitor. It has demonstrated its ability in promoting tumor regression of many different KRAS mutation types in mouse KRASG12X xenograft models [11]. Moreover, it did not affect the growth of normal tissues and cells [11]. Currently, a Phase I clinic trial aiming at figuring out the appropriate dose and efficacy of RMC-6236 is being carried out. The success of PanRAS inhibitors can be broadly beneficial for a wide range of cancers.

5. Drug Resistance

From the “undruggable” perception to a wide range of drugs with different mechanisms, great progress was made in targeting KRAS in recent years. Even so, it remains difficult for current drugs to overcome KRASi resistance in tumor cells. For sotorasib and adagrasib, which have been widely used for NSCLC treatments, most patients will have tumor recurrence due to acquired KRASi resistance in several months. In fact, most of the current research on KRASi resistance indicates different causes. This suggests that the mechanism of acquired KRASi resistance is very complex.

5.1. Binding site changes

For KRASG12C covalent inhibitors, the most easily detectable resistance mutations are those at the binding site. During tumor evolution, the KRAS protein may produce new secondary mutations. These mutations alter the structure of the binding site so that the inhibitor can no longer bind to the KRAS protein. For example, mutations of amino acid residues at positions 12, 68, 95, and 96 of the KRASG12C are critical to sotorasib and adagrasib binding. This demonstrates the limitations of covalent binding inhibition on tumor cells.

5.2. Abnormal activation of downstream signaling pathways

Most KRAS inhibitors block the signaling pathways by keeping the KRAS protein in an inactive state. In acquired KRASi-resistant tumor cells, abnormal activation in downstream signaling pathways is often observed, such as the reactivated RAF-MEK-ERK pathway. It indicates tumor cells can generate a novel mechanism to bypass KRAS inhibition. This may be caused by wild-type KRAS, HRAS, and/or NRAS, or there may be other pathways that do not rely on the KRAS protein. Proteostasis is indispensable for the proliferation of cancer cells. The research by Lv et al. shows abnormal activation of downstream signaling pathways restored inositol-requiring enzyme 1α (IRE1α) phosphorylation and stability, which is very important in restoring proteostasis [12]. Aberrant activation of downstream signaling pathways suggests that combination therapies of different KRAS inhibitors may be required for a better outcome.

6. Methods against resistance

6.1. Combination Medications

To solve the problem of resistance to KRAS inhibitors, a lot of research is looking to develop powerful combination therapies. A popular direction is to block the upstream signaling pathway for KRAS activation. For instance, taking sotorasib with the epidermal growth factor receptor (EGFR) inhibitor preliminary achieved a good outcome [13]. There are also studies that attempt to control tumor cell proliferation by cutting off downstream signaling pathways of KRAS. Inhibition of IRE1α can significantly improve the time to acquisition of KRASi resistance [12]. Besides targeting the RAS signaling pathway, KRASi can also be combined with other oncology treatments, including some conventional chemotherapy. PD-1 inhibitor is one of the newest cancer treatment drugs. It helps kill tumor cells by restoring and protecting T-cell immune function. There is a considerable possibility that the combination of PD-1 inhibitor and KRASi will become a powerful therapy.

6.2. New Drug Mechanism

Besides all the drugs mentioned earlier in the article, there are many prototype compounds based on completely different mechanisms. Some of them, although only in the very early stages of research, have shown great potential. For instance, some molecules can promote the degradation of mutant KRAS proteins. Some research focuses on using T cell receptors to label tumor cells with KRAS mutations, which can eventually kill tumors by activating immune responses.

Small interfering RNA (siRNA) is a new technique. It inhibits the production of disease-causing proteins by specifically binding to mRNA sequences and interfering with mRNA translation. Current siRNA drug Inclisiran has demonstrated that siRNA drugs have good efficacy and can be maintained for very long. The main challenge in siRNA research is to develop reliable delivery mechanisms. Nanoparticle-based delivery platforms have been developed for delivering KRAS siRNA, and it is very likely to be a feasible treatment strategy.

7. Summary

KRAS is one of the most common mutated genes in tumors. For a long period of time, it was impossible to treat tumors by targeting KRAS. The situation did not change until sotorasib and adagrasib produced positive inhibition outcomes by establishing covalent binding to KRAS protein. To address the resistance problem, inhibitors with better selectivity and efficacy, such as divarsib, were developed. Research into KRAS-related signaling pathways led to new drugs like MRTX0902. Besides, drugs targeting KRASG12D and other mutant subtypes are also under investigation. Although the actual mechanism of acquired KRASi resistance remains unclear, new combination therapies and innovative drugs can probably alleviate the problem of drug resistance to a large extent. As can be seen, drugs targeting KRAS have a great prospect. The technology and research progress presented in the review might help readers inspire new ideas for the development and improvement of KRAS drugs.

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