Targeting MEK: attempting to overcome Cancer resistance to RAS-MAPK therapies

MEK: tentativa de superar a resistência ao Cancro nas terapias RAS-MAPK

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Saúl Landeira Cancela
Biotechnology Graduate from the University of León
Institution: University of León
Address: C/ Álvaro López Núñez, 32, Bajo, León
E-mail: slandc00@estudiantes.unileon.es

ABSTRACT
MAP kinases pathway is a well-known signal transduction pathway activated by several mitogens, resulting in cell proliferation, growth and migration. Nevertheless, mutations in its kinases upregulate this pathway, leading to development of cancer. Among other strategies, MEK (a kinase belonging to MAP kinases pathway) has been identified as a therapeutic target in some types of cancer, including colorectal and lung cancers. Mostly, MEK inhibitors are able to overcome the resistance that tumor cells have acquired to other drugs, but novel strategies look for combining MEK inhibitors with other blockers, obtaining promising results. In this review, we will discuss the current methods of combating cancer resistance, focusing in the central role of MEK.

Keywords: Cancer, CRC, drug resistance, MEK, NSCLC, RAS-MAPK pathway.

RESUMO
A via da MAP kinases é uma conhecida via de transdução de sinal activada por vários mitógenos, resultando em proliferação celular, crescimento e migração. No entanto, as mutações nas suas kinases upregulam esta via, levando ao desenvolvimento do cancro. Entre outras estratégias, a MEK (uma kinase pertencente à via da MAP quinases) foi identificada como um alvo terapêutico em alguns tipos de cancro, incluindo os cancros colorrectal e pulmonar. Na sua maioria, os inibidores de MEK são capazes de superar a resistência que as células tumorais adquiriram a outros medicamentos, mas novas estratégias procuram combinar os inibidores de MEK com outros bloqueadores, obtendo resultados promissores. Nesta revisão, discutiremos os métodos actuais de combate à resistência ao cancro, concentrando-nos no papel central do MEK.

Palavras-chave: Cancro, CRC, resistência aos medicamentos, MEK, NSCLC, via RAS-MAPK.
1 INTRODUCTION

Cancer is a non-specific concept used in Medicine and Biology to describe a group of illnesses consisting of decontrolled proliferation of cells in an organism. Unfortunately, this pathology is fairly common in human population, representing one of the main causes of death in the world. According to World Health Organization, nearly 10 million people died in 2020 due to the effects of cancer and other 10 million cases were diagnosed in the same year. Mostly, lung and colorectal tumors predominated among last year defunctions (WHO, 2020).

In view of these alarming data, a deeper approach concerning cancer development and consequent therapies should be made. While it is true that many groups have been doing research regarding this issue, cancer presents multiple pathways to progress and depends on many factors, some of which are still to determine. In other words, the mechanisms that this pathology follows are too complex to fit in one paper. Therefore, I have decided to focus this review in RAS-MAP kinases pathway and its therapeutical potential.

2 RAS-MAPK PATHWAY

Mitogen-activated protein (MAP) kinases pathway comprehends a cascade of phosphorylation of proteins which leads to transcription of genes involved in cell proliferation, migration and growth, when stimulated by mitogens such as growth factors (Robinson and Cobb, 1997). Proteins participating in the cascade are mostly kinases, which have the ability to phosphorylate the following protein, thus activating it and transducing the initial signal triggered by the mitogen (Figure 1).
However, when a mutation is present in a kinase, MAP kinases pathway becomes constitutively activated, resulting in tumor appearance (Cobb and Goldsmith, 1995).

Among other proteins of the via, MEK has stood out as a potential therapeutic target. Despite having a low mutation rate in cancer, it plays an important role as a convergent spot of several transduction signals with similar functions in cancer development. If a drug aimed specifically MEK, it would certainly detain cell cycle and stop decontrolled cell proliferation (Sebolt-Leopold and Herrera, 2004). This has been the modus operandi for researchers since the Ras-MAP kinases pathway discovery. Some drugs developed in the last decade, like selumetinib and pimasertib, targeted MEK and had applications in lung and colorectal cancer, respectively (Zhao and Adjei, 2014).

These illnesses turn particularly interesting due to the characterization of cancer resistance to RAS-MAP kinases therapies. Through some mechanisms, tumor cells can overcome the inhibition of MEK and still perform gene transcription
and, consequently, proliferation. I will discuss both types of cancer and the role of the MAP-kinases pathway, as well as the novel strategies being used to enhance previous therapies focusing on MEK.

3 LUNG CANCER

Non-small cell lung cancer (NSCLC) represents the majority of lung cancers and has poor prognosis, due to its late detection. This pathology can affect epithelial or squamous cells in the lungs, and it is often found in old, smoking patients, although some young non-smokers can also suffer from it. Depending on NSCLC and patient characteristics, different approaches in their treatment can be made (Thomas et al., 2015).

Lately, and in contrast with classical chemotherapy, new therapies focusing on MAP kinases pathway have been attempted. Given that initial strategies inhibiting cell receptor EGFR were barely effective because of tumor resistance development, MEK became a novel target for NSCLC treatment (Martinelli et al., 2017).

Single MEK inhibitors as sorafenib were used in NSCLC patients. Decrease in tumor proliferation was observed as a result of avoiding the effects of upregulation of upstream kinases. Nevertheless, using only one MEK inhibitor usually turns long-term ineffective due to cell resistance attributed to feedback mechanisms and activation of other pathways (Martinelli et al., 2017). This unexpected result demands a restructuration of this specific approach to cancer deceleration.

Recent-years therapies are based in combination of MEK inhibitors with drugs targeting either MAP kinases or external pathways elements, based in synergy phenomenon. Blocking the via in two different points will prevent the feedback mechanisms that escape single-drug treatments (Han et al., 2021). The most promising strategy consists in matching MEK and immunotherapy. Research has shown that MEK inhibitors provide a suitable environment to enhance anti-PD-1/PDL-1 activity, usually performed by monoclonal antibodies. PD-1 and PDL-1 are immunoregulator proteins whose union triggers cell proliferation and survival (Della Corte et al., 2019). To this day, this therapy appears to be effective and has overcome single therapy resistance, but it still needs to be developed.
4 COLORECTAL CANCER

Regarding colorectal cancer (CRC), its frequency has increased substantially during the last decades, representing one tenth of cancers in the Western Hemisphere. It consists in decontrolled growth of epithelial cells of the large intestine, starting as a small adenoma and then developing as a malign tumor (Kuipers et al., 2015).

Speaking of molecular patterns in CRC, they are quite alike to those in NSCLC, since similar mutations have been observed in both types and MAP kinases pathway plays the same role in tumor resistance. Well-known monoclonal antibody cetuximab, which inhibits EFGR receptor, has shown some efficacy, but frequently, downstream mutations in RAS escape this therapy (Garrett and Eng, 2011; Normanno et al., 2009).

As a consequence, novel approaches have suggested combining two drugs aiming different points in the pathway, imitating what had been done in NSCLC and other types of cancer. In this case, some research lines tried the simultaneous application of cetuximab with MEK inhibitors. Fortunately, this attempt has led to more satisfactory results than using cetuximab solely (Van Cutsem et al., 2011).

Following this line, another group has gone one step further and has applied a triple-spot therapy in patients suffering a specific type of CRC, called BRAFV600E. This cancer is due to a single mutation in BRAF gene, which encodes for the first kinase of the MAP kinases pathway. Contrary to what it was believed, single inhibition of BRAF with dabrafenib was not enough to stop the development of tumor progression. As a result, the group studied what would happen when inhibiting two points in the via with two different drugs. As it is shown in Figure 2, somehow cancer is able to overcome double treatment. However, triple treatment using dabrafenib, panitumumab and trametinib detains long-term tumor growth in 15% of patients. Those drugs are in charge of blocking BRAF, EFGR (a growth receptor) and MEK, respectively, showing the tremendous potential of combining medicines aiming RAS-MAP kinases pathway (Corcoran et al., 2018).
Figure 2. Efficacy of D+P, T+P, and D+T+P in patients with BRAFV600E colorectal cancer. Progression-free survival (PFS) of cohorts undergoing different treatments. Dabrafenib (D), panitumumab (P) and trametinib (T) (Corcoran et al., 2018).

5 CONCLUSION

In this review, the issue that cancer represents in modern society has been addressed, as well as the need to look into a better understanding of this pathology. The comprehensive study of tumor molecular basis can shed light on possible future solutions to this problem and it is clear the huge potential some signaling pathways, like RAS-MAP kinases, have on it.

Though original single-target therapies showed promising results in cancer prognosis, they have been proved to be inefficient due to tumor resistance. Given the complexity of escape mechanisms that these cells present, evidence suggests aiming different proteins related to MAP kinases pathway simultaneously, so that drug resistance can be avoided.

Focusing on MEK, a group of novel treatments which combine two or more inhibitors has been developed. In NSCLC and CRC, several strategies have blocked multiple spots on the via, always defining MEK as the main objective. Despite having great success, not all types of cancer can be treated with these methods. Therefore, some research still needs to be done to clarify and improve these therapies.


World Health Organization (WHO). https://www.who.int/es/news-room/fact-