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Targeting Changes in the RAF-MEK Pathway

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Abstract

One of the most frequently mutated oncogenic pathways in cancer is the MAPK pathway. Although RAS mutations are the most common MAPK changes, changes in downstream components of the pathway, such as the RAF and MEK genes, offer promising therapeutic opportunities. Other alterations in the RAF and MEK genes may provide rarer, but tractable, targets in addition to BRAFV600 mutations, for which several approved therapeutic regimens, exist. Recent studies, however, have demonstrated the complexity of MAPK signalling and highlighted the fact that different alterations in these genes may have strikingly different properties. Understanding the distinct functional properties of specific RAF and MEK alterations, as discussed here, will be critical for developing effective therapeutic approaches for these targets.

Keywords: Oncogenic • Gene • Mutation • Signalling

Introduction

The MAPK signalling pathway is essential for many important cellular processes. Its dysfunction causes uncontrollable cellular proliferation, survival, and dedifferentiation. As a result, the MAPK pathway is altered or improperly activated in the vast majority of cancers. MAPK signalling is activated in physiologic conditions by activation of RAS proteins (KRAS, NRAS, and HRAS), a family of small guanine triphosphatases (GTPases) that integrate signals from a variety of upstream sources, most commonly activated receptor tyrosine kinases. These upstream signals activate guanine nucleotide exchange factors, such as son-of-seven less (SOS), which catalyse the conversion of RAS-bound guanine triphosphate (GDP) to guanine triphosphate [1].

The frequency of genomic alterations in the MAPK pathway decreases as one move downstream in the pathway: RAS mutations occur in 22% of human tumours, BRAF mutations in 7%, MEK mutations in 1% of cases, and ERK mutations are extremely rare. The degree of ERK activation produced by changes upstream in the pathway (for example, RAS mutations) is frequently constrained by negative feedback signals, whereas those further downstream escape negative feedback regulation and can result in more profound activation of pathway output. Differences in ERK-responsive gene expression between BRAFV600E mutants (strongly activating) and RAS mutants are seen in papillary thyroid cancers, where expression of ERK-responsive genes important in iodide transport can be easily assayed [2].

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In contrast, "amplifier" changes are dependent on upstream activity and enhance the downstream signal to ERK. Activating changes strongly activate ERK and are usually mutually exclusive, whereas amplifying changes frequently co-occur with other activating mutations upstream in the pathway. Interestingly, the frequency of activating mutations decreases as one moves downstream in the pathway, while the proportion of amplifying alterations increases; activating alterations in downstream components of the pathway, such as MEK or ERK, would result in extremely high levels of output because they evade feedback signals, and may thus have a selective disadvantage. Understanding the distinct signalling properties of specific RAF and MEK alterations is critical for developing strategies to combat them [4].

Literature Review

Independent of upstream signalling, RAF-independent mutants strongly activate MEK and ERK. This class of mutants is distinguished by in-frame deletions within a stretch of amino acids that eliminate a powerful negative regulatory segment of MEK1. This region corresponds to a similar 3-C loop in the MEK kinase domain, resulting in a shortened loop that keeps the kinase in an active "C-in" conformation. When this negative regulatory domain is removed, auto phosphorylation of the activating serine residues at positions 218 and 222 occurs, resulting in an increase in MEK kinase activity. Indeed, the expression of these MEK1 mutants can drive strong MAPK signalling and cellular transformation in "RAF-less" cells, which have conditional ARAF, BRAF, and CRAF (RAF1) alleles that can be deleted by CRE, recombines, demonstrating their independence from RAF activity [5].

Another clinical strategy for targeting class II mutations is to use newer RAF inhibitors that act as RAF dimer inhibitors or RAF dimer breakers. In these models, these inhibitors can disrupt signalling from active BRAF dimers and suppress MAPK signalling. Because second-generation RAF inhibitors have only recently entered the clinic, it is unclear whether they can achieve clinical responses in tumours with class II BRAF mutations [6].

Downstream MAPK signalling inhibitors retain their ability to suppress MAPK signalling in the presence of class III mutations. However, it is unclear whether downstream MAPK signalling inhibition will be sufficient to achieve clinical tumour responses or whether targeting RTK signalling in the tumour will be required. As previously stated, no patients with class III BRAF mutations responded to the ERK inhibitor ulixertinib, most likely due to high RAS activation in these tumours, which attenuates the effect of the ERK inhibitor.

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Discussion

Thus, targeting the upstream signal for which the class III mutations serve as a "amplifier" is one promising strategy for tumours with class III BRAF mutations. This is easiest to do in tumours with wild-type RAS and dominant RTK signalling. Colorectal cancers with class III BRAF mutations, for example, have been linked to increased sensitivity and survival with anti-EGFR antibodies. Thus, targeting the dominant RTK may be a viable and manageable strategy for tumours with class III mutations. Because tumours do not always have a single dominant RTK and may receive signals from multiple RTKs, SHP2 inhibitors, which block a key common effector target used by multiple RTKs, are an alternative approach to blocking upstream signalling [7].

Conclusion

The MAPK pathway is important in human cancer and is inappropriately activated in a large proportion of cancers via a variety of mechanisms. However, due to the MAPK pathway's complex signalling biology, distinct alterations in downstream pathway components, such as RAF and MEK, can have dramatically different signalling properties. In recent years, careful biochemical and functional studies have been critical in elucidating the critical nuances of MAPK signalling in order to create key opportunities for therapeutic development. In the meantime, future clinical trials of novel strategies targeting RAF or MEK alterations should include careful pharmacodynamics evaluation via paired pre-treatment and on-treatment tumour biopsies to determine the specific signalling effects of each therapy on its target.

Acknowledgement

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Conflict of Interest

There is no conflict of interest by author.

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