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Review

The role of KRAS in Macropinocytosis and its implications of Multi-Drug Resistance in Cancer

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Abstract

KRAS is one of the most frequently mutated oncogenes in cancer and is involved in various tumorigenic processes. Among its diverse roles, KRAS mutations have been shown to upregulate macropinocytosis, a form of endocytosis that allows cells to engulf extracellular fluid and its contained solutes, subsequently supporting the increased need for the growth and proliferation of cancer cells. The nutrient uptake function of macropinocytosis was initially described within the framework of KRAS-driven pancreatic tumors. Although constitutive macropinocytosis can be induced by activating mutations of proteins that are commonly found in cancer, KRAS-induced macropinocytosis constitutes a fundamental area of research due to the high occurrence of mutated KRAS in cancer (~1/3 of all cancers). Furthermore, KRAS-mutated macropinocytosis not only contributes to tumorigenesis but also plays a critical role in developing resistance to treatments, as it was found to be implicated in Multi-Drug Resistance (MDR) in cancer cells. This mini-review aims to synthesize current knowledge of mechanisms of KRAS-mutated macropinocytosis briefly and examines the relationship between KRAS and macropinocytosis in the light of its role in cancer progression and drug resistance, highlighting therapeutic implications, targeting potential vulnerabilities and outlining clinical advancements in pertinent therapies.

1. Introduction

Cells can perceive and interact with their extracellular environment through various mechanisms which can be clathrin-mediated endocytosis, caveolae-mediated endocytosis, endocytosis, phagocytosis, and macropinocytosis. Macropinocytosis is a unique one, as it is a type of endocytosis known for its high internalization efficiency and non-specific fluid-state uptake. It enables the engulfment of large quantities of extracellular fluids, which has been harnessed especially with the advancement of nanomedicine, using this phenomenon to improve the cellular uptake of nano-sized

drug delivery systems[1,2]. Macropinocytosis can occur spontaneously in some cells or be activated by growth factors, Toll-like receptors, or chemokines in others. However, it becomes significantly increased in cancers characterized by metabolic dysregulation, especially in KRAS-driven cancers which are notorious for their aggressive malignancies[3]. Given that the *RAS* family of oncogenes (*KRAS, HRAS, NRAS*) have mutations most frequently in cancers and regulate key signaling pathways driving tumor progression, it was also found that KRAS actively induce nutrient uptake including glucose, lipids, and albumin, via macropinocytosis[4] Modifying cancer cells' metabolism and energy production processes, including KRAS-driven macropinocytosis, is crucial for meeting their energetic needs and facilitates growth and proliferation, making it a key focus for various therapeutic strategies[5].

1.1 ***Background on KRAS function and mutations***

KRAS is a well-studied proto-oncogene that encodes GTPase signal-transducing protein called KRAS, and it ranks as one of the most commonly mutated oncogenes in human cancers. It is presented in approximately 25-30% of all human cancers, playing a pivotal role in driving cancer progression as well as in the development of various human cancers[4,6]. KRAS mutations are particularly implicated in several aggressive cancer types and constitute more than 80% of pancreatic cancers and more than 30% of colorectal, cholangiocarcinoma, and lung adenocarcinomas[7]. KRAS proteins belong to a larger family of guanosine triphosphate (GTP)-binding proteins that serve as “molecular switches” act by alternating between an inactive state bound to guanosine diphosphate (GDP) and an active state bound to GTP. Under physiological conditions, KRAS is bound to GDP. However, upon binding to GTP stimulated by growth factor, KRAS undergoes conformational changes resulting in its activation. Subsequently, it activates the downstream of the Raf-MEK-ERK pathway signaling axis. It stimulates cell proliferation and increased glycolysis, which is prevalent in cancer cells to fulfill the increased nutrient requirements of proliferating cancer cells. Activated mutations of the KRAS gene interfere with alternating between the active/inactive state resulting in cell transformation. It was also linked to biological therapies targeting epidermal growth factor receptors[8].

KRAS activation also induces Phosphoinositide 3-kinase (PI3K) effectors, stimulating cell proliferation, migration, and survival. These two most validated classes of RAS

effectors which are the RAF/MEK/ERK (MAPK) and PI3K/AKT/mTOR pathways are key drivers in RAS-mediated oncogenesis[9].

During tumorigenesis, specific mutations of RAS particularly at codons 12, 13, and 61 cause constitutive RAS-GTP binding and subsequent activation of downstream effectors resulting in uncontrollable cell proliferation and survival[10]. Moreover, mutated forms of KRAS also rapidly exchange GDP for GTP, which is the preferable substrate, thus inducing the active state[8,11].

As for the KRAS functions, it acts as a key sensor that triggers the activation of multiple signaling molecules, enabling the transmission of transducing signals to the nucleus; this activation interferes with essential cellular networks including cell differentiation, proliferation, apoptosis, and chemotaxis. The signaling pathway of the KRAS protein is initiated when epidermal growth factor (EGF) binds to its receptor leading to the activation of tyrosine kinases and subsequently transmitting the activation signal to the nucleus through MAPKs and PI3K/AKT-mediated pathways[12].

In recent years, oncogenic RAS has been linked to metabolic alterations in many processes, including increased glucose uptake, changes in the utilization of glucose intermediates, glutamine addiction, and increased metabolic scavenging pathways such as autophagy and macropinocytosis to meet the enhanced energetic and biosynthetic requirements of cancer cells[9,13,14].

2. Overview of Macropinocytosis and its role in Cancer Metabolism

Macropinocytosis, a common endocytic process found in the eukaryotic cells, was first visually captured by Warren Lewis in 1931 using microcinematography[15]. Unlike other endocytic routes, macropinocytosis enables the nonselective internalization of large quantities of extracellular fluids[16]. The process of macropinocytosis is based on the actin cytoskeleton to form a ring of actin that polymerizes beneath the plasma membrane. This ring extends outward as a circular ruffle. It eventually closes at the top through constriction, leading to membrane fusion that generates a large endocytic vesicle (0.2–5 μm) known as a macropinosome. The macropinosome cargo is then degraded in the lysosomal vesicles. This uptake pathway plays a crucial role in supporting cancer cell metabolism by facilitating nutrient absorption, allowing cancer cells to survive particularly in cancer types with nutrient-scarce microenvironments[17].

One of the distinctive features of macropinocytosis is the fact that it can be stimulated

by growth factors including EGF[18]. As it was mentioned earlier, KRAS is a downstream signaling molecule of the EGFR pathway that could be activated by either growth factor stimulation or oncogenic mutation, leading to the stimulation of different signal transduction pathways, including Rac and Cdc42, that are also necessary for macropinocytosis[6] . Several recent studies have shown that nutrient deprivation itself can promote macropinocytosis, in addition to several mutations of specific signaling pathways in tumor cells that were found to stimulate constitutive macropinocytosis[17,19]. However, RAS-induced macropinocytosis constitutes a major research interest due to the significant prevalence of mutated RAS in cancer[9].

3. The role of KRAS in Macropinocytosis Regulation

KRAS mutations have been shown to play a crucial role in promoting macropinocytosis, especially in nutrient-limited environments[6]. Further, membrane ruffling followed by macropinocytosis, was induced by injecting activated RAS protein into fibroblasts. It is inhibited to striking extents when phosphatidylinositol(3,4,5)-trisphosphate (PIP3) production is reduced with drugs or genetically[20,21]. RAS and PIP3 regulate the early events of macropinosome formation, since RAS activates class-I phosphatidylinositol 3-kinases (PI3Ks) which are major regulators of the actin cytoskeleton, these enzymes in turn produce the membrane lipid PIP3[22].

The mechanistic insights into how KRAS mutations enhance the macropinocytosis process in cancer cells are still limited. The findings of Ramirez et al. to reveal regulators of macropinocytosis, conducting a full genome short interfering RNA (siRNA) screen, point out that the vacuolar ATPase (V-ATPase) is a crucial activator in KRAS-induced macropinocytosis through the stimulation of protein kinase A and Rac1. Oncogenic KRAS induces translocation of V-ATPase from intracellular membranes to the plasma membrane. The accumulation of V-ATPase at the plasma membrane is essential for the plasma-membrane association of RAC1, a small GTPase crucial for the membrane ruffling required for macropinocytosis[9,23,24].

Yao et al. determined Syndecan 1 (SDC1, also known as CD138) as an innovative effector of macropinocytosis, which was found to be upregulated at the cell surface by KRAS in the doxycycline-inducible KRAS mouse model of PDAC[25]. It was found that transient siRNA suppression of KRAS reduced macropinocytosis in $KRAS^{G12D}$ $KRAS^{G12V}$, and $KRAS^{G12C}$ mutant cell lines. Surprisingly, suppression of KRAS did not

reduce macropinocytosis in the KRAS^{G12R}-mutant pancreatic ductal adenocarcinoma (PDAC) lines, this underscores the significance of considering distinct mutant alleles of KRAS to stratify patients with PDAC appropriately[24,26]. Taking the mechanisms through which KRAS mutations enhance macropinocytosis, opens significant vulnerabilities to leverage macropinocytosis and its associated pathways for therapeutic strategies in cancers with KRAS mutations[27].

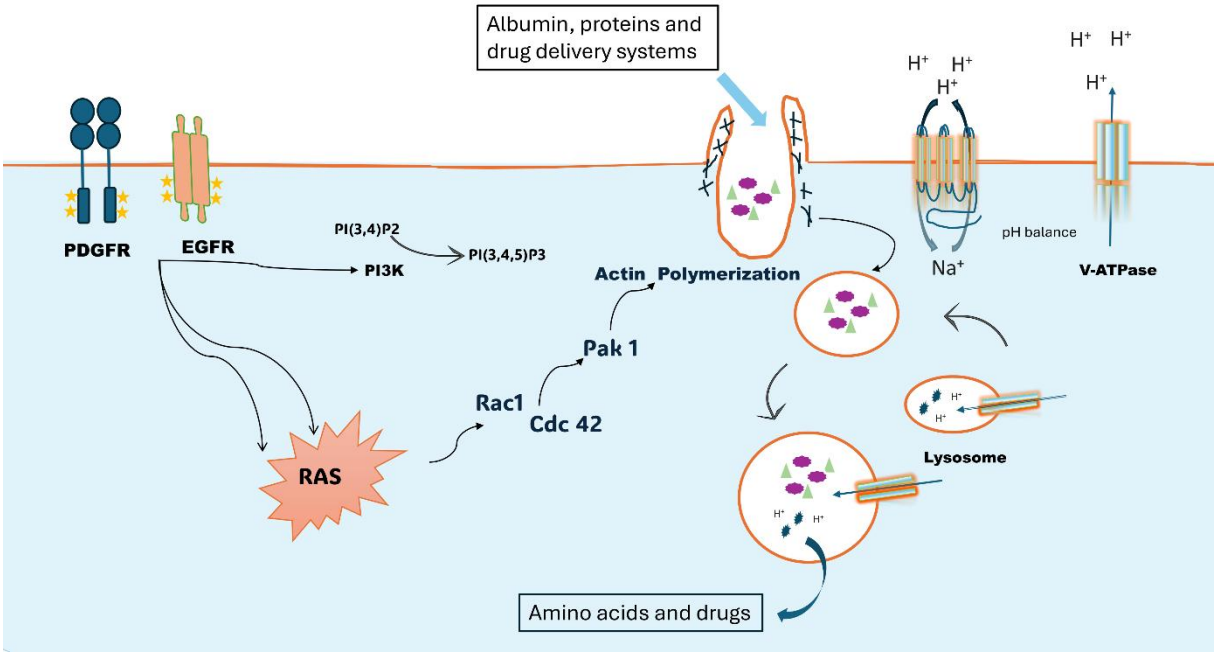

Figure 1.: Schematic representation of the formation of macropinosomes governed by RAS activation. Growth factor stimulation or oncogenic mutation of RAS leads to membrane ruffling and macropinocytosis. Pak1 - p21-activated kinase 1; Rac1 - Ras-related C3 botulinum toxin substrate 1; V-ATPases - vacuolar H+-ATPase; PI3K – phosphoinositide 3-kinase[28].

4. The role of KRAS-mutated Macropinocytosis in Cancer Multi-Drug Resistance and Therapeutic Perspectives

Multidrug resistance (MDR) comprises a major challenge to effective therapeutic interventions in cancer therapies. One aspect of cancer resistance includes metabolic reprogramming to support rapid growth[29]. Metabolic rearrangements considered a hallmark of cancer, have also been found to make tumors less responsive to treatments. This includes, tumors with KRAS mutations, which are known to exhibit improved survival mechanisms that contribute to chemotherapy resistance. Additionally, KRAS-mutated macropinocytosis significantly influences cancer MDR by enhancing nutrient uptake, thereby supporting survival in the scarce tumor microenvironment. Notably, a genetic approach that selectively targets

macropinocytosis in tumor cells demonstrates that the macropinocytosis process drives both tumor growth and drug resistance, underscoring the significant role of macropinocytosis in MDR[30].

The strong independence of RAS-driven cancers to scavenge nutrients to support their metabolism shows a potential vulnerability that can be exploited therapeutically[16].

Ongoing clinical trials focus on various aspects of targeting KRAS-driven macropinocytosis, from directly inhibiting KRAS mutations to exploring novel approaches that inhibit the macropinocytosis process. One area of research involves using macropinocytosis-specific inhibitors, such as 5-(N-Ethyl-N-isopropyl) amiloride (EIPA) and imipramine, as therapeutic agents in pathological processes involving macropinocytosis, where they have presented effectiveness in pre-clinical mouse pancreatic cancer models[31] . Another approach is directly targeting KRAS mutations, particularly the $KRAS^{G12C}$ mutation, with inhibitors such as Sotorasib and Adagrasib. These drugs aim to block the mutated KRAS protein, reducing tumor growth and potentially decreasing the tumor's reliance on macropinocytosis for nutrient uptake. These KRAS inhibitors are being tested both as monotherapies and in combination with other treatments such as chemotherapy or immune checkpoint inhibitors[34] .

Considering the fact that the activation of KRAS mutations triggers several signaling pathways, including the PI3K-AKT-mTOR and the MAPK-EPK pathways, that contribute to the development of drug resistance, the targeting of oncogenes or their downstream mediators is anticipated to be lethal to metabolically addicted cells while sparing normal cells[32,33]. Interestingly recent findings demonstrated the potential efficacy of Adagrasib, a novel $KRAS^{G12C}$ inhibitor, in reversing MDR associated with KRAS mutations[34]. Furthermore, KRAS mutations have been found together frequently with altered drug uptake caused by the upregulated expression of drug efflux transporters, which actively pump chemotherapy drugs out of cancer cells[35]. Additionally, many KRAS-mutant colorectal cancer cell lines show higher ABCB1 expression[36,37]. Indeed, many studies have sought to exploit the phenomenon of KRAS-enhanced macropinocytosis using various approaches, one of which involves conjugating albumin with drug molecules. This strategy provides a much wider therapeutic window compared to the free drug[38].

Another strategy to leverage macropinocytosis employs nanoparticles and cyclodextrin-based drug delivery systems to enhance drug delivery efficiency. These

nanoparticles can be engineered to encapsulate anticancer agents, especially with cyclodextrins which hold a high potential for efficient and localized cancer treatment[39]. It was also found that cyclodextrins can alter drug permeability by inhibiting the function of efflux pumps[40].

Additionally, various combination therapies are currently being explored, with research revealing promising therapeutic options. For instance, the inhibition of macropinocytosis, when combined with metabolic interventions like asparagine depletion, has demonstrated synergistic anti-tumor effects in KRAS mutant colorectal cancer. *In vivo*, studies have shown that this combined approach significantly suppresses tumor growth in KRAS mutant colorectal cancer models. The inhibition of macropinocytosis deprives cancer cells of the ability to scavenge extracellular nutrients, while asparagine depletion further exacerbates nutrient stress, pushing the cells into a metabolic crisis. This dual blockade effectively disrupts the adaptive mechanisms of cancer cells, holding potential as a novel treatment for KRAS-driven malignancies, and offering hope for overcoming the limitations of current therapies[41].

Another innovative approach within this framework of combination therapies involves stimulating macropinocytosis of peptide-drug conjugates (PDCs) through DNA-dependent protein kinase (DNA-PK) inhibition. By targeting this process, therapies like MPD1,a macropinocytosis-targeting peptide-drug conjugate (PDC), have been developed to treat KRAS mutant cancers, enabling the direct drug delivery into cancer cells. However, the success of these treatments is often blocked by DNA-PK, which helps the cancer cells repair the damage caused by therapy. DNA-PK inhibitors, such as AZD7648, can stop this repair process, allowing the efficacy of the treatment. Combined therapy with MPD1 and AZD7648 achieves a complete response in a KRAS-mutant xenograft model by boosting drug uptake, apoptosis, and counteracting DNA repair resistance. This synergistic approach underscores the potential of combining MPD1 with AZD7648 for effective treatment[42].

5. Conclusion

KRAS-mutation tumors have a strong dependence on macropinocytosis which reveals significant insights into the metabolic vulnerabilities that can be exploited therapeutically. The crucial role of nutrient scavenging in supporting tumor growth, survival, progression, and developing multi-drug resistance highlights the importance of a deep understanding of the molecular pathways governing KRAS-driven

macropinocytosis. By exploiting these metabolic dependencies and integrating related therapies, future research may develop a more well-structured roadmap to target KRAS tumors. Ongoing clinical trials are actively investigating KRAS inhibitors and macropinocytosis modulators, with combination strategies likely to be a key area of focus. However, significant challenges remain in terms of selective targeting. Understanding the detailed molecular mechanisms and identifying reliable biomarkers for patient selection and treatment response are crucial for optimizing these therapies. These questions must be addressed to improve the effectiveness of therapies and provide new hope for patients with KRAS-mutant cancers.

Data Availability Statement:

All measurement data are available at the corresponding author in case of further requests.

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