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Spotlight

Tumor growth going *FAR* with KRAS *FAR*nesylation-induced phase separation

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RAS at the plasma membrane relay signals from cell-surface receptors to intracellular pathways. In *Cell*, Wang et al.[1] show that farnesylation drives KRAS cytoplasmic condensation, contributing to its maturation. They identify statins as candidates to overcome resistance to KRAS-targeted therapies.

In 1982, in what *Nature* called "the year of oncogene," independent discoveries placed the RAS GTPases at the center of cancer biology.[2] Since then, Kirsten RAt Sarcoma viral oncogene homolog (KRAS), neuroblastoma RAS viral oncogene homolog (NRAS), and Harvey rat sarcoma viral oncogene homolog (HRAS) have remained among the most studied yet therapeutically elusive targets in cancer. RAS mutations are found in nearly 30% of human cancers, where the protein is "locked" in a constitutively active, guanosine triphosphate (GTP)-bound state that drives sustained mitogenic signaling.[3] Despite decades of effort, RAS proteins were long considered "undruggable," and although mutant-specific inhibitors targeting KRAS-G12C and pan-RAS inhibitors are now transforming treatment options, resistance persists to be a problem. This highlights a fundamental gap: while RAS signaling outputs are extensively characterized, its intracellular processing and maturation remain poorly understood.

RAS signal transduction begins when a growth signal is received by receptor tyrosine kinases (RTKs, e.g., EGFR), which relay it as phosphorylation to adaptors such as Growth factor receptor-bound protein 2 (GRB2) and Son of Sevenless (SOS-1), switching RAS into its active, GTP-bound form and triggering the RAF/MEK/ERK cascade or auxiliary routes like AKT. Before reaching the membrane, however, KRAS must undergo post-translational processing, i.e., farnesylation of its C-terminal CAAX motif, followed by proteolytic cleavage by Ras-converting enzyme 1 (RCE1) and methylation.[4] These modifications enable stable membrane association, a prerequisite for signaling, and KRAS is thought to organize into membrane nanoclusters that serve as critical signaling platforms. However, signaling can also arise from intracellular compartments.[5]

Writing in *Cell*, Wang and colleagues uncover an unexpected layer of KRAS regulation: farnesylation, long considered solely a trafficking modification, also drives KRAS into cytoplasmic, liquid-like condensates that aid its own post-translational processing. This study reveals a previously unrecognized role for biomolecular phase separation in the KRAS life cycle, with broad implications for KRAS-mutant cancers.[1]

Wang et al. found that colon cancer tissues exhibited markedly higher levels of cytoplasmic KRAS protein aggregation than normal tissue samples, and importantly, patients with more of these aggregates in cancer tissues showed advanced disease, increased metastasis, and poorer overall survival.[1] To characterize this aggregation, the authors used multiple orthogonal biophysical approaches such as high-resolution imaging, solubility assays, fluorescence recovery after photo bleaching (FRAP), and *in vitro* reconstitution of purified KRAS to show that it forms dynamic, liquid-like condensates. These assemblies displayed several liquid-liquid phase separation (LLPS) properties, including fusion and fission behavior, rapid FRAP recovery, detergent solubility, and sensitivity to 1,6-hexanediol. Altogether, these experiments establish that KRAS undergoes liquid-liquid phase separation distinct from its membrane or endoplasmic reticulum localization.[1] The authors next mapped the structural features driving condensation. Deletion of the hypervariable region (HVR), predicted as the most intrinsically disordered region, substantially reduced condensate formation. Mutagenesis across the HVR pinpointed cysteine 185 (C185), its farnesylation site, as particularly critical for LLPS. Mutating this residue or pharmacologically inhibiting farnesylation both blocked condensation, which could be rescued by restoring hydrophobicity via acyl chains added to the HVR-deletion mutant, arguing that farnesylation-driven hydrophobicity is a key determinant of KRAS phase separation.[1]

The authors next examined the role of condensation in signaling. Following epidermal growth factor (EGF) stimulation, KRAS condensates increased in number while remaining cytoplasmic, suggesting that phase separation, and thus processing, is dynamically regulated during pathway activation. Indeed, the non-farnesylated C185S mutant failed to efficiently activate downstream signaling, a defect again rescued by restoring hydrophobicity.[1] To gain insight into the composition of these assemblies, the authors performed proteomic analysis of condensate-enriched fractions and identified the prenyl-processing enzyme RCE1 as a prominent condensate-associated factor enriched in condensates but not in bulk cellular fractions. Super-resolution microscopy subsequently confirmed RCE1 localization within KRAS condensates. These findings suggest that rather than inert cytoplasmic aggregates, KRAS condensates are transient maturation hubs that spatially coordinate processing before delivery to signaling-competent membranes marking this as the first evidence that protein farnesylation can drive LLPS to control its own processing and signaling.[1]

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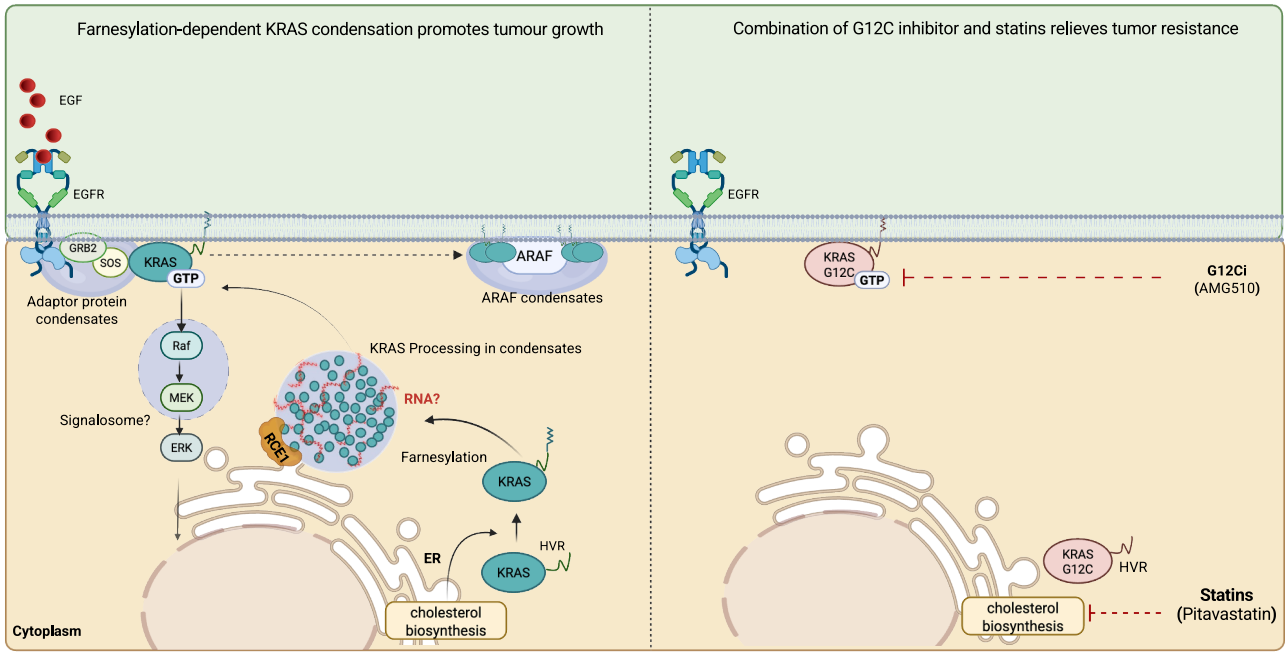

Figure 1. Farnesylation-dependent KRAS condensation links oncogenic signaling to a therapeutically targetable cholesterol metabolism

(Left) Following synthesis, KRAS undergoes C-terminal processing, including farnesylation of its hypervariable region (HVR), and assembles into dynamic condensates that facilitate its maturation by modifying enzymes such as Ras-converting enzyme 1 (RCE1) at the endoplasmic reticulum (ER) before trafficking to the plasma membrane. There, EGF stimulation activates EGFR signaling, relayed through GRB2 and SOS1/2 to load KRAS-GTP and activate downstream MAPK signaling. Li et al.[7] showed that MAPK pathway kinase ARAF can condense at the plasma membrane with activated KRAS aiding cancer progression

(Right) Oncogenic KRAS-G12C sustains downstream signaling and tumor growth but remains dependent on mevalonate-pathway-derived intermediates required for farnesylation. Statins inhibit cholesterol biosynthesis, reducing KRAS prenylation and condensate formation and thereby limiting the pool of signaling-competent KRAS. Combining a KRAS-G12C inhibitor such as sotorasib (AMG 510) with a statin such as pitavastatin therefore suppresses complementary steps in KRAS activation and can overcome therapeutic resistance. Dashed arrows indicate proposed indirect connections, and question marks denote mechanisms that remain to be established.

The link between condensation and prenylation led the authors to investigate its clinical implications. Screening FDA-approved compounds identified statins as potent inhibitors of KRAS condensates.[1] Pitavastatin, an 3-hydroxy-3-methylglutaryl (HMG)-coenzyme A (CoA) reductase inhibitor, efficiently dissolved assemblies even under strong EGF stimulation. Supplementing mevalonate-pathway intermediates restored condensate formation, confirming the effect was specific to prenylation inhibition. Using KRAS-knockout cells reconstituted with wild-type KRAS, an LLPS-deficient ΔHVR mutant, or a hydrophobicity-rescued Lyn-KRAS construct, the authors found that both KRAS deletion and HVR disruption impaired tumor growth in mouse xenografts, whereas wild-type and Lyn-KRAS restored tumorigenic potential. Similar results held for oncogenic KRAS-G12C, where disrupting farnesylation reduced tumor growth and restoring hydrophobicity rescued it.[1] Finally, in patient-derived xenografts with acquired resistance to the G12C inhibitor sotorasib (AMG 510),[1,6] pitavastatin re-sensitized tumors to sotorasib, an effect abolished in tumors expressing acylation-rescued Lyn-KRAS, indicating that pitavastatin anti-tumor activity depends specifically on disrupting farnesylation-driven condensation (Figure 1).[1]

Together, these experiments support a model in which farnesylation serves a role beyond membrane anchoring. This hydrophobic modification drives transient liquid-like condensates that facilitate KRAS processing before productive signaling, redefining an early, spatially regulated step of the KRAS life cycle.[1] The findings also open a therapeutic avenue. By identifying statins as inhibitors of KRAS condensation, Wang and colleagues suggest that targeting the mevalonate pathway could complement existing KRAS-directed therapies.[1] This raises a broader clinical question that, as millions of patients worldwide take statins chronically for cardiovascular disease, do they show reduced incidence, delayed onset, or improved outcomes of KRAS-mutant cancers? Answering this will require carefully controlled retrospective and prospective studies, but the possibility of repurposing an inexpensive, widely prescribed drug class is compelling. Furthermore, similar to KRAS, NRAS and HRAS share similar post-translational processing but differ in trafficking, membrane residence, and nanoscale organization.[4] It will be important to determine whether farnesylation-dependent condensation is a general feature of RAS maturation or particularly prominent for KRAS, given that NRAS is a prominent oncogene in cancers such as melanoma. Isoform-specific differences in condensate composition or lifetime could offer a new framework for understanding their distinct tissue-specific oncogenic activities. More broadly, this study shows that a lipid modification long viewed as a membrane-targeting signal can also act as a

biophysical regulator of oncogenic signaling,[1,4] expanding farnesylation's role from a trafficking determinant to a driver of spatial organization. Several signaling components, including SHP2-, GRB2-, and RAF-family kinases, have separately been linked to condensate-like assemblies during pathway activation,[8,9] raising the open question of whether such structures function as bona fide signalosomes that tune mitogen-activated protein kinase (MAPK) amplitude, duration, or specificity. Reported interactions between KRAS and small nucleolar RNAs further raise the possibility that RNA binding contributes to KRAS condensate organization, as observed for other phase-separating proteins.[10]

DECLARATION OF INTERESTS

The authors declare no competing interests.

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