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Mastermind Behind RAS and EGFR Mutations and a Novel Ferroptosis Inhibitory Approach

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ABSTRACT

Here we present a novel theory of reversing RAS/ EGFR mutation downstream activations and vicious cycle on activating oncosuppressors by inhibition of autophagy and induction of ferroptosis. The use of off label drugs and natural compounds specifically to target the genes involved in this pathway are explored and discussed. We present a case of treated patient with non small cell lung cancer using such approach successfully, and propose that application of such method can increase the survival of patients with RAS mutated tumors at least at hypothesis. Further clinical trials for lung cancer and other solid tumor types are recommended.

Keywords

RAS mutation, Ferroptosis, Autophagy.

Background

Recently a survival mechanism was discovered in certain rats that is based on activation of a gene called FOXO. This gene induction reduces the metabolism and keeps the animal alive while starving. Similar to hibernation, this pathway has improved animals survival when starving in winter). At the same time we know that another member of FOX gene family, called FOXP [1] has been found to increasingly play role in inhibition of FBXW7 oncosuppressor gene by it's induction. The FBXW7 oncosuppressor gene has been discovered as a very influential gene in carcinogenesis, in almost all types of tumors, specifically in melanoma, LUNG CANCER, thyroid cancer and colorectal cancers, where RAS/EGFR mutation could be driving the tumor growth. (RAS is a downstream of EGFR) We also have found a direct correlation of FOXP4 gene and RAS/ EGFR mutation as it appears that RAS activates the FOXP4. This vicious cycle is essentially what makes RAS tumors specifically difficult to treat as there is positive feedback loop between FOX/ FBWX7 and RAS/ EGFR. Interestingly inhibition of FOXP4, through a process called ferroptosis, can reverse this cycle. As such one can conclude that inhibition of ferroptosis can be a vital step in treatment of RAS/ EGFR mutated tumors [2-5].

In prior literature I also have discussed mechanisms involved with inhibition of autophagy and induction of apoptosis. It also appears that some of the compounds (excluding cytotoxic drugs) that inhibit autophagy can also induce ferroptosis. Again one can conclude that both inhibition of autophagy and induction of ferroptosis are correlative of similar pathways. This said, the literature in this area is inconclusive as some data suggests that autophagy is required for the process of Ferroptosis by providing Fe ++. One for example form of autophagy is ferritinophagy [6-8]. Also Mitophagy produces elements needed for ferroptosis and lipophagy produces lipid peroxidation required for ferroptosis [1,9-14]. Our data suggests that ferroptosis inhibits autophagy and this is exactly how it suppresses cancer. As such using compounds that inhibit both autophagy and induce ferroptosis are recommended.

The mechanisms in which autophagy protects cancer development and ferroptosis contributes to carcinogenesis are both before the mutation occurs. As soon as there is oncogene mutation or an onco suppressor inactivating mutation, this effect be comes completely reverse. Autophagy contributes to cancer progression and so does inhibition of ferroptosis [15-19].

TP53 gene mutation reduces the ferroptosis efficacy as in normal circumstances TP53 sensitizes the cell to ferroptosis. As such one

can conclude that in patients with mutated TP53 tumors (almost half of all solid tumors) ferroptosis needs to be resensitized/ activated as part of treatment strategy [20-24]. Ferroptosis also activates the tumor immune response by releasing the ROS. One other important factor is the acetylation of H3K56 acetylation (epigenetic involvement): Activation SIRT6→ Reduced H3K56 acetylation→ accumulation of ROS→ Ferroptosis

AMPK activation and m Tor inhibition both activate autophagy, and therefore it should be kept in mind that in tumors driven by RAS, the use of everolimus could be ineffective, as the downstream of RAS is AMPK and by using everolimus similarly this pathway indices autophagy and by product of PI3KCA.

RAS/ EGFR→AMPK→PI3KCA<← Inactivation of M-TOR [25-27]

Other genes involved in ferroptosis include: M-Tor, NRF-2, Stat3, Beclin 1 [28], AMPK [25,29-38] and ATF-4 [26]. When mTOR activity is elevated, it suppresses the initiation and progression of autophagy. MTORC1, in particular, inhibits the formation of autophagosomes. NRF-2 activation due to cellular stress leads to modification of Keap-1 and intracellular activation of oxidative stress response genes and autophagy [39-45].

STAT3 binds to consensus DNA response elements and controls their expression, serving as a major negative regulator of ferroptosis in gastric cancer [46-49].

Compounds of interest: Annexin A10, Polyphyllin VII (PPVII), a pennogenin isolated from the rhizomes of Paris polyphylla, was detected to suppress the growth of gastric cancer by inducing autophagy-mediated ferroptosis, We already have discussed Sulfasalazine, Plaquenil, (HCQ in combination with Trametinib or TMZ in retinoblastoma, melanoma and gliomas) [50-52], Ultrasmall iron oxide nanoparticles (USIONPs), Tetrahydroxystilbene (TG1), 3 bromopyruvate /3BP, available in injectables at research (I have used it in patients) [53], Ailanthone (AIL), a monomer extracted from the traditional Chinese medicine Ailan, available as a skin product [54], novel carrier-free nano-drug called nanoparticle ferritin-bound Erastin and rapamycin (NFER), also in the nanomedicine field, Zhang et al. created an incredibly tiny polyvinylpyrrolidone (PVP)–Fe–Cu–Ni–S (PVP-NP) nano-agent which can synergistically trig ger ferroptosis and autophagy in photothermal cancer therapy [55,56].

In general inhibition of Wnt pathway, indices ferroptosis, Curcumin, Quercetin, Artemisinin, Statins, EGCG, and Chinese herbs (ERIANIN, ERASTIN, SHIKONIN, BAICALIN), Capsaicin, Ginseng [57], Salinomycin, Sulfasalazine [58], all induce Ferroptosis. Acetaminophen (oral or IV), at high dose has been studied substantially in reduction of tumor growth specifically in RAS positive disease with impactful response (more than 20 percent positive response rate) as sole therapy or combination with other chemotherapy agents. To negate the liver toxicity effects of AAP, NAC and Fomepizole has been used in subjects in study with protective function against normal cells (and no effect on tumor cells). The mechanism of action is reduced Cysteine and by product Glutathione. (glutathione is an inhibitor of ferroptosis).

Methods and Materials

Case study

64 years old female with history of left upper lobe adenocarcinoma of the lung, status post lobectomy (VATS) on 6/29/22, has T2 tumor, + 2 nodes, and resected 4.3 cm incidental finding in her CXR. She was advised to do chemo and targeted therapies, which she refused. She referred to us for evaluation and treatments. Initial assessment showed her molecular profiling had manifested EGFR as well as Notch2, Rb1, Myc, MDM2. PDL-1 negative.

Her labs were drawn before therapy. We discussed her VEGF and TGF both being elevated. VEGF was 341 which was alarming, and could pointed into dissemination of disease. Immediately she was started on daily infusions of epigenetic therapies, consisting of quercetin and Vitamin C. Her labs were repeated after 10 IV therapies. Her VEGF dropped down to 259 on 9/19/22. Further she received additional 10 treatments and her VEGF repeated which dropped down to 89 measured on 10/20/22, and her TGF came down from 8948 to 6888. She continued the IV therapies at our clinic with superior results.

She did not change her diet or start any other therapies. She started Erlotinib at 50 mg per day (standard dose 150 mg/d), on 11/2022, and continued the IV epigenetic therapies per protocol once every week, and her labs monitored. She was restaged which all showed positive response to therapy with no metabolically avid disease/ findings. In November 2024, her scan showed an increased metabolic activity of left upper mediastinal LN, at internal mammary chain with SUV of 4.2. She had tapered down the therapies to once a month at this point.

Immediately she was restarted on once weekly treatments and Hydroxychloroquine (as inhibitor of autophagy) [59] was added to her regimen to improve her response at 200 mg daily. Her scan was repeated after about 12 months in November 2025 which showed positive response to the therapy. The scan showed improved response with reduction of the size and metabolic activity of the left upper mediastinal lymph node. (14x 8 mm from 20x10 mm and SUV down from 4.2 to 2.4). There was also a perivascular node 11x10 mm with SUV of 2.2.

Currently she continues the treatments with us with no sign of progression of disease. This sustainable response is unexpected with non traditional care as well as combination with low dose erlotinib. At best scenario erlotinib works for less than 12 months at 150 mg a day. This patient has accomplished positive response for over 3 years with 1/3rd dose of EGFR inhibitor without the need to switch to second or third generations of this drug class. She has not encountered any side effects of the therapies.

Case study 2

63 years old female with history of stage four colon cancer

diagnosed in 2024 status post hemicolectomy, and FOLFOX+ Avastin regimen with initial positive response, status post progressive disease manifested with liver metastatic disease in 2025 in her scan, started on Xeloda then switched to Stivarga and further Irinotecan, again with progressive disease manifested in the size and activity of her liver lesions, last on Lonsurf. His scan was performed prior to starting the therapies with us which showed:

History of colon cancer status post partial colectomy. 2. Multiple hypermetabolic hepatic lesions measuring up to 6.6 cm with maximum SUV 15, compatible with metastatic disease. 3. Multiple hypermetabolic abdominal lymph nodes measuring up to 10 mm with maximum SUV 6 at the peripancreatic region, compatible with metastatic disease. 4. Multiple mildly hypermetabolic pulmonary nodules measuring up to 9 mm with maximum SUV 3.2 in the right lower lobe, compatible with metastatic disease

This scan showed a significantly larger and more active lesions compared to the one patient had in January 2026. For example the SUV activities had increased from 11 to 15 and the size of largest tumor to 6 cm in liver. This progression was despite use of Lonsurf.

At this point patient was referred to us and her labs taken which showed extensively elevated tumor markers and liver enzymes. Her liquid biopsy was also performed which showed extensively high mutated allele frequencies (MAF) of several alterations, including KRAS A 146 T, APC, PI3KCA, ESR amplifications, FBXW7, TP53, and PTEN (Figure 1).

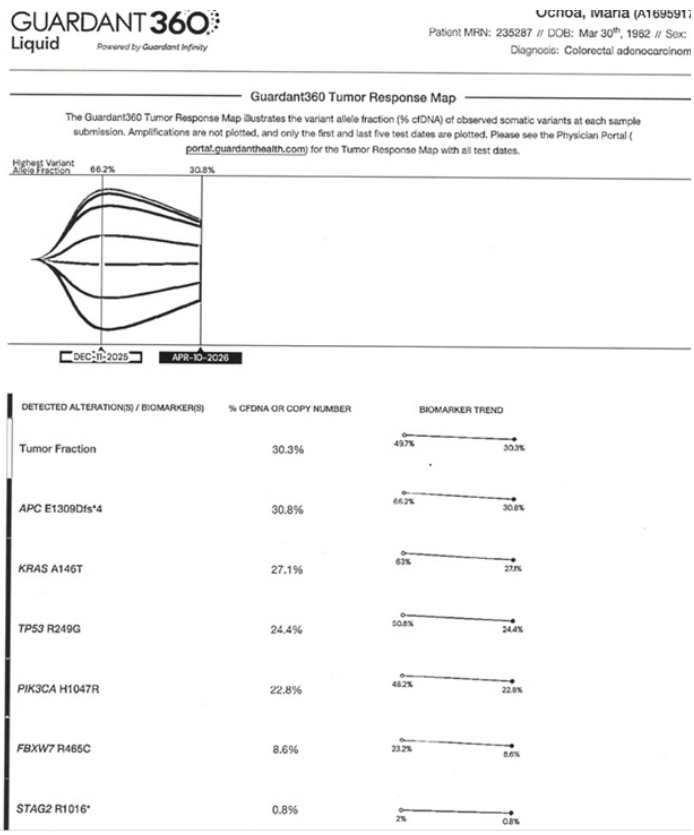
KRAS A146T	⊖ Avutometinib+defactinib ⊗ Cetuximab, Panitumumab	Yes	26.9%
PIK3CA H1047R	⊖ Alpelisib, Capivasertib, Inavolisib	Yes	20.2%
PTEN Deletion, exon 1	⊖ Capivasertib	Yes	0.3%
TP53 R249G	None	Yes	23.0%
FBXW7 R465C	None	Yes	9.1%
STAG2 R1016*	None	Yes	1.0%
TP53 P151T	None	Yes	0.1%
APC E1309Dfs*4	None	Yes	32.8%
ESR1 Amplification	None	Yes	Medium (++)

Figure 1: Liquid biopsy (Guardant 360).

Patient received Daily IV MTET therapies for three weeks and further her labs were repeated,. The MTET protocol consisted of Rifampin, HQC and Crestor as well as IV Nano quercetin. Her labs showed:

All her tumor markers dropped significantly with the therapy. CA 19.9 normalized at 34, CEA dropped from 3188 down to 2734!!

c DNA has dropped significantly from 49.7 percent to 30 percent on tumor fraction, 30 percent from 66.2 percent on APC, 27 percent down from 63 percent on KRAS, 24 percent from 50 percent on TP53, 22 percent from 48 percent on PIU3KCA, 5 percent from 23 percent on FBXW7,....



Liver enzymes dropped ALK-P from 476 to 380. AST from 56 to 48, ALT from 53 to 30. She has gained some muscle mass as well with improved creatinine from 0.34 to 0.45. CBC all normalized.

She continues the treatments at our clinic with superior results.

Conclusion

Since RAS/EGFR mutated tumors respond to inhibitory function of autophagy modulators, addition of ferroptosis inducers seem to be critically effective in tumor management to current standard therapies. (cytotoxic or targeted therapies) and based on our experience, clinically feasible and meaningful. Larger clinical trials are warranted.

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