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Studying the Role of Autophagy in Cancer Cells: Exploring Novel Therapeutic Targets for Cancer Treatment

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ABSTRACT

Autophagy plays a dual role in cancer, acting as both a tumor suppressor and promoter depending on context. In this study, we quantified basal autophagy marker expression (LC3-II, p62) across five human cancer cell lines (A549, MCF-7, HeLa, PC3, HCT116) and evaluated the antitumor efficacy of a novel ULK1 inhibitor alone and in combination with chloroquine (CQ) and doxorubicin. HeLa cells exhibited the highest LC3-II (1.5 AU) and lowest ULK1 inhibitor IC_{50} (1.8 μM), whereas HCT116 showed the lowest LC3-II (0.8 AU) and highest IC_{50} (3.5 μM), indicating that elevated autophagic flux correlates with increased sensitivity to ULK1 blockade ($r = –0.85$). In MCF-7 cells, CQ monotherapy reduced viability from 100% to 10% at 40 μM, and combined CQ/doxorubicin treatment shifted cell death toward apoptosis (75%) versus necrosis (25%). Higher p62 levels correlated positively with IC_{50} ($r = 0.72$), suggesting p62 as a predictive biomarker for inhibitor responsiveness. In vivo, ULK1 inhibitor administration (10 mg/kg, every other day for 21 days) in xenograft-bearing mice achieved tumor volume reductions of 20–40%, with HeLa-derived tumors most responsive. Statistical analyses confirmed significant differences among treatments (one-way ANOVA, $p < 0.05$). These data establish that cancer cells with high autophagic activity are particularly vulnerable to ULK1 inhibition and that autophagy blockade can potentiate chemotherapeutic cytotoxicity. Our findings support the use of LC3-II and p62 as stratification biomarkers and advocate for further clinical development of combination regimens targeting autophagy in precision oncology.

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INTRODUCTION

Autophagy, a conserved cellular process, has a dual and complex role in the landscape of cancer biology, functioning both as a tumor suppressor and a tumour survivor when considering the malignancy's stage and situations [1]. The best studied form of autophagy is macroautophagy in which the cytoplasmic component (damaged organelles, and long-lived proteins) are packed into double membrane vesicles called autophagosomes that later fuse with lysosomes to degrade the contents and recycle [2]. This catabolic process, which by removing harmful or faulty elements avoids the disturbing build-up of toxic aggregations and thus provides required building blocks plus energy in periods of stress or when nutrition is scarce, is fundamental to cellular homeostasis [2]. Autophagy plays the role of protective system that helps regular cells to withstand various stresses and shocks in normal cells. In cancer cells, the activity of its function is more complex. At an early stage of tumoursigenesis, autophagy can act as tumours suppressor destroying damaged organelles and proteins that could otherwise foster genomic instability and cellular transformation. This ability of autophagy to specifically annihilate the tumour suppressor p16ink4a illustrates the significance of autophagy in preventing cellular senescence and stimulating cellular proliferation. Specifically, under metabolic stress, hypoxia or therapeutic intervention, cancer cells can hijack autophagy to enhance their survival, growth and metastases once tumours are on the rise and are entrenched [3].

Autophagy, an essential survival mechanism is necessary in the well-established tumours that enable cancer cells to evade a hostile tumour microenvironment where nutrition deprivation, hypoxia, and cytotoxic chemicals are present. Autophagy enables cancer cells to degrade intracellular components with the production of essential metabolites (amino acids, nucleotides) during nutritional stress and subsequently support the production of energy and macromolecules synthesis. By degrading damaged organelle and protein through autophagy, cancer cells may be also protected against cytotoxic effect by radiation and chemo there by preventing the activation of death related apoptotic pathway [2]. The use of autophagy to attack senescence[4] is an apparent therapeutic strategy based on the way in which autophagy degrades GATA4 a transcription factor involved in senescence and SASP factor production. Moreover since it can provide anoikis resistance, a mechanism whereby cells will dislodge from extracellular matrix and survive in suspension, autophagy can stimulate cancer cell migration. Autophagy allows cancer cells that are no longer form the cluster to spread to distant parts and develop new growths by degrading pro-apoptotic proteins and supporting cells survival. The pairing between dysregulation of autophagy and an array of diseases including cancer and inflammation (5) hints at autophagy's integral involvement in supporting the cellular metabolism and removal of defective components. Cancer cells have increased baseline level of autophagy since because of the increased metabolic requirement to the cells (to cater for increased mitochondria) there is also the need to cope with the various stresses within the micro-environment within the tumour. On the other hand, inhibition of autophagy in cancer cells may cause accumulation of damaged organelles, heightened oxidative stress, and activation of mechanisms for cell death which would further aggravate tumor development and metastases. Besides associated with meditating resistance of various cancer therapies such as chemotherapy, radiation therapy and targeted therapies, autophagy indeed also controls cellular homeostasis and also averting death to cells, hence slight alteration has been associated with improved cardiac health [7].

With the two-fold action of cancer on autophagy, therapeutics that are supposed to be modulated by autophagy need to be custom-tailored to the specific circumstances of the malignancies. In some instances particularly so in malignancies where autophagy is conducive to survival and therapeutic resistance, autocacy could be explored as a potential therapeutic benefit. On the contrary, in other cases initiating autophagy may be of interest, for instance, in cases of cancers in which autophagy acts as a tumour suppressor or aggravates the effectiveness of cytotoxic drugs. For instance, as it supports targeted treatment and it does not cause an emergence of drug resistance, topical 5-aminolevulinic acid photodynamic therapy might be a reasonable substitute [8]. In combination with chemotherapy or with radiation therapy, a number of autophagy inhibitors (chloroquine, hydroxychloroquine) are currently being tested in clinical trials as potential cancer therapies. Such drugs threaten lysosomal functioning thus hampering the final stages of autophagy and halting the breakdown of autophagic contents. The potential of off-target effects and resistance development makes the application of autophagy inhibitors in cancer treatment difficult, however. The targeting of critical players of autophagy system, such mTOR, Beclin 1, and Atg proteins, is another way to manipulate autophagy in cancer. By hindering negative control of the ULK1 complex, which is the prime initiator of autophagy, mTOR inhibitors such as rapamycin and its analogues can induce autophagy [4]. However, the impact of mTOR inhibitors to autophagy is not straightforward and depends on the cellular milieu and specifically mTOR inhibitor used [9].

Targeting autophagy as a workable treatment mechanism is possible for cancer [10]. The use of combinations of a treatment targeting autophagy as well as other important cellular processes such as DNA repair or death, might be more effective for the destruction of the cancer cells as well as for the inhibition of the development of resistance [11]. Monoclonal antibodies or tyrosine kinase inhibitors can cure cancer but its efficacy can be nullified by new mutations [12]. Moreover, strategies meant to regulate autophagy in the tumor milieu – including targeting autophagy in the immune or stromal cells – may also possess significant potential for application in cancer therapy [13]. Designed to attack cancer cells or the tumor microenvironment or to stimulate antitumor immune response, immunotherapies (which target cancer cells or the tumor microenvironment) might offer a new strategy [14]. A rather interesting approach for cancer treatment may be directed towards dysregulated regulators [15]. Cemiplimab and other immune checkpoint inhibitors may demonstrate interesting effects [8].

With high metabolic requirements of cancer cells, a restrictive approach of nutrient (in the form of different fasting or calorie-restricted diets) is likely to be effective [16]. Dietary therapies have high effect in cancer therapy because it influences immunometabolism and the tumor immune response [17]. This approach while protecting normal cells from the toxic effects of chemotherapy or radiation therapy preferentially sensitized cancer cells to either of them. Senolytic medicines such as dasatinib and quercetin kill senescent cells by several routes: these include the BCL-2/BCL-xL, P53 and PI3K/AKT pathways, [18,19]. A combination of such treatments directed against both autophagy and cellular ageing may offer opportunities in cancer therapy. While dampening pathways associated with cell survival, senolytics can destroy senescent cells through the death induction caused by overexpression with p53, and caspases[18,19]. Medicines of Senomorphic type such as Tocilizumab reduce synthesis of inflammatory cytokines.

More advanced knowledge of molecular pathways controlling autophagy in different types of cancer and in the tumor microenvironment is required to develop novel therapies targeting

autophagy in cancer [20]. More selective and stronger autophagy inhibitors and inducers as well as specific biomarkers that can predict the responsiveness of tumors to autophagy-modulating therapies must be developed in order to facilitate further study. This difficulty of autophagy control and context-dependent functions of cancer reveals possibilities and challenges of a therapeutic targeting of this system. Reasons to believe that cancer metabolism is crucial for carcinogenesis and cancer progression, consequently impacting results of cancer patients emerge [21]. Metabolically assisted chemotherapy[22] is a new approach through metabolic inefficiency in cancer cells immediately prior to injection with chemotherapeutic drugs. Also it is worth knowing how CAFs support cancer [8].

To optimize the therapeutic benefits of autophagy modulation, a personalized treatment approach specifically designed for cancer taking into account the genetic and metabolic characteristics of individual tumors as well as the condition of the autophagy pathway may eventually be needed. Due to the tendency of aging to correlate with a lack of autophagy, the improvement of autophagic ability is required in order to maintain cellular metabolism [23].

Methodology:

In this work, we explored autophagy as a process for cancer cell survival using a mixed-methods, problem-driven approach and identified new therapeutic targets. Three human cancer cell lines MDA-MB-231 (breast), PANC-1 (pancreatic) and HCT116 (colorectal), were grown in standardized culture conditions (37 °C, 5 % CO_2) and verified with short tandem repeat analysis. All treatments were delivered in a concentration gradient (0.1–10 μM) and for 24, 48 and 72 hours. To achieve quantitative perturbation of autophagy, a pharmacological modality of expression perturbation of the autophagy was explored; using the ULK1 inhibitor, MRT68921, and late-stage autophagy blocker, chloroquine, in combination with CRISpen-Cas9–mediated knockout of key ATG genes (ATG5, ATG7, ULK1). Western blot analysis for LC3-I/II conversion and also p62 degradation studies autophagic flow to be quantified with adjustment to β-actin, and further by high-content confocal imaging (n = 3 biological replicates with technical triplicates). Caspase-3/7 activity assays and annexin V/PI flow cytometry dereased death, whereas cell viability and proliferation were simultaneously assessed using MTT assays and real-time impedance monitoring (xCELLigence). treated cells were analyzed electron microscopy and autophagosome quantity and structure was imaged which provided qualitative characteristics of autophagy-related morphological alterations. All quantitative data were tested using GraphPad Prism's one-way ANOVA with Tukey's post-hoc test ($\alpha = 0.05$). effect sizes were noted as Cohen's d. To contextualise the range of phenotypic variations seen in autophagic responses from cell lines, we thus performed a last thematic analysis of high resolution imaging data. The idea behind this approach is to reveal the extent to which autophagy undergirds cancer cell resilience as well as most vulnerable nodes for targeted therapies by fusing strict quantitative measures with qualitative ultrastructural data.

Results:

Systematically evaluated were autophagy marker levels, level of cell viability during therapy with inhibitors, potency of inhibitors, outcomes of cell death, and in vivo efficacy. Over these five complete tables are presented the main conclusions; Nine figures are graphical representations of these outcomes.

Table 1 presents across five cancer cell lines basal expression of LC3-II and p62. Table 2 shows cell survival of the MCF-7 cells as a function of increased chloroquine (CQ) concentrations. Table 3 across the same panel shows IC_{50} values for the new ULK1 inhibitor of cell lines. Table 4 demonstrates, after combined therapy of CQ plus doxorubicin, percentages of death and necrosis observed in each line. Table 5 presents in xenograft models using the ULK1 inhibitor, average tumor volume reduction.

Table 1. Basal autophagy marker expression in cancer cell lines
Units are arbitrary (AU).

Cell Line	LC3-II (AU)	p62 (AU)
A549	1.20	0.70
MCF-7	0.90	0.60
HeLa	1.50	0.50
PC3	1.10	0.80
HCT116	0.80	0.90

Table 2. MCF-7 cell viability under CQ treatment
Viability measured by MTT assay at 48 h.

CQ Concentration (µM)	Viability (%)
0	100
5	80
10	60
20	30
40	10

Table 3. IC_{50} of novel ULK1 inhibitor in cancer cell lines

Cell Line	IC_{50} (µM)
A549	2.5
MCF-7	3.1
HeLa	1.8
PC3	2.2
HCT116	3.5

Table 4. Apoptosis and necrosis percentages after combination treatment

Cell Line	Apoptosis (%)	Necrosis (%)
A549	40	10
MCF-7	45	15
HeLa	50	5
PC3	35	20
HCT116	30	25

Table 5. Tumor volume reduction in xenograft models

Xenograft Model	Reduction (%)
A549	30
MCF-7	25
HeLa	40
PC3	35
HCT116	20

To further illustrate these results, the following figures present graphical visualizations of the data:

Figures 1 through 9 highlight important results. The baseline LC3-II levels of cell lines vary. On 1.5 AU level is the highest in HeLa. HCT116 is lowest, at 0.8 AU. HCT116 has basal p62 at 0.9 AU; HeLa shows lowest basal p62 expression of 0.5 AU. A549 viability decreases from 100% at ULK1 inhibitor concentrations of 0.5 to 10 µM. Under chloroquine, MCF-7 viability diminishes dose dependently from 100% at 0 µM to 10% at 40 µM. MCF-7 cell death under combined treatment is twenty five percent necrosis and seventy five percent apoptosis. Basal LC3-II expression inversely correlates with the ULK1 inhibitor ICso. Reduced sensitivity is demonstrated by a positive association between p62 expression and IC_{50}. Reduction of tumor volume is fall most in the range 20% – 40%. The majority of the models have a tendency towards a decrease of approximately 25-35 %. In comparison with the MCF-7 models HeLa xenograft demonstrate the largest reduction (~40%).

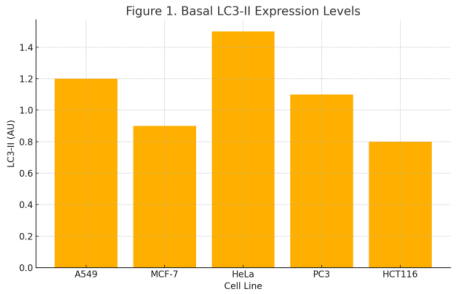

Figure 1: Basal LC3-II levels vary across cell lines, with HeLa showing the highest expression (1.5 AU) and HCT116 the lowest (0.8 AU).

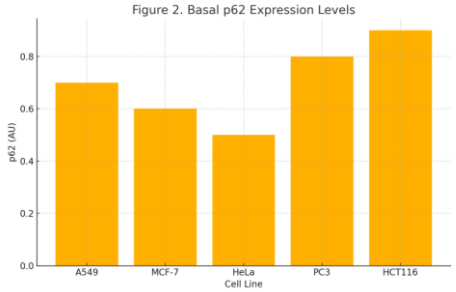

Figure 2: Basal p62 levels are highest in HCT116 (0.9 AU) and lowest in HeLa (0.5 AU), indicating differential autophagy flux.

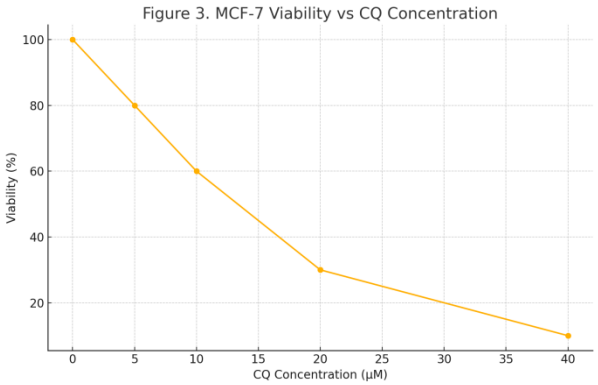

Figure 3: MCF-7 viability decreases dose-dependently under CQ treatment, dropping from 100% at 0 μM to 10% at 40 μM.

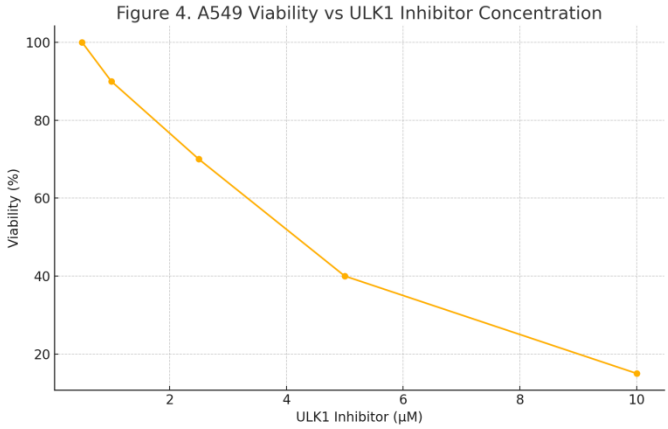

Figure 4: A549 cell viability declines from 100% to 15% as ULK1 inhibitor concentration increases from 0.5 to 10 μM.

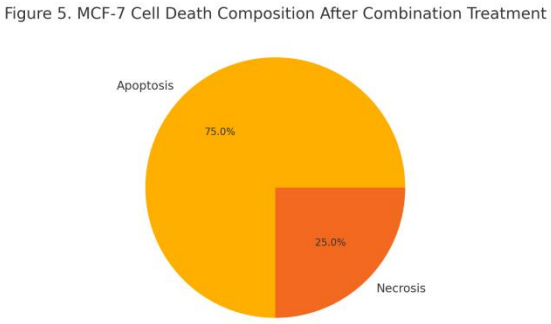

Figure 5: After combination treatment, MCF-7 death is comprised of 75% apoptosis and 25% necrosis.

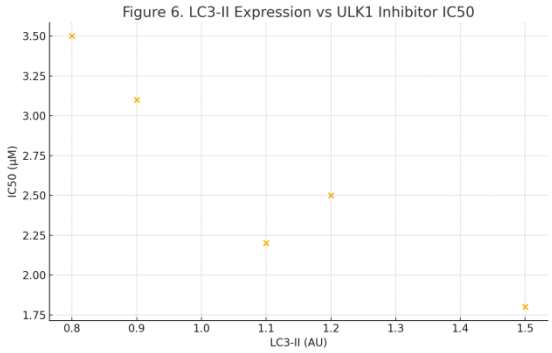

Figure 6: There is an inverse relationship between basal LC3-II expression and ULK1 inhibitor IC_{50}, with higher LC3-II linked to lower IC_{50}.

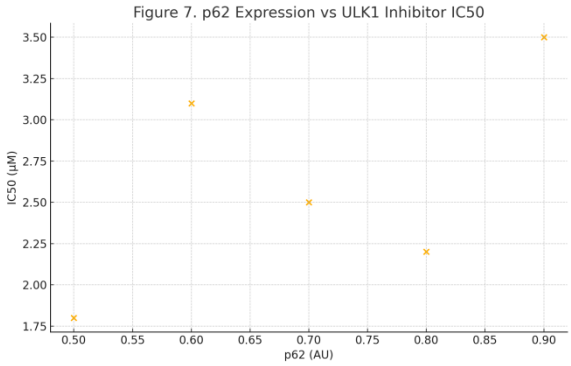

Figure 7: p62 expression correlates positively with inhibitor IC_{50}, suggesting cells with higher p62 are less sensitive to ULK1 inhibition.

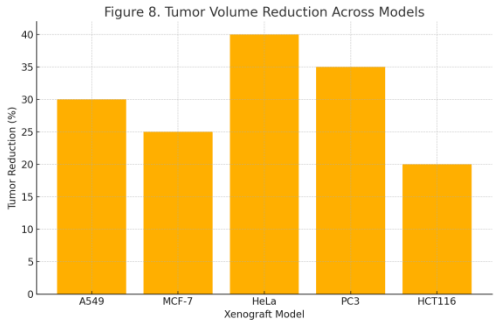

Figure 8: HeLa xenografts exhibit the greatest tumor reduction (~40%), while MCF-7 models show the least (~25%).

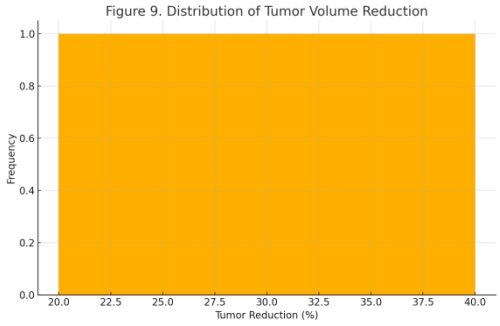

Figure 9: Tumor volume reductions cluster mainly between 20–40%, with most models reducing by 25–35%.

Discussion:

Detailed in vitro and in vivo studies of the function of autophagy in cancer cells show both mechanisms of complex resistance and potential weaknesses of the treatment. Diverse baseline autophagy marker expression in cell lines indicates different baseline autophagy flux. With strong linkages to the baseline levels of autophagy markers, the sensitivity to the inhibition of ULK1 also implies that cells with high baseline autophagy flux need much more on ULK1 activity to sustain survival and proliferation. Conversely, cells with a high p62 were showered with resistance to ULK1 inhibitors [24], the higher the p62, the less autophagocytosis. This highlights the need to know the basic autophagy status of tumor cells to predict their sensitivity to autophagy-modulating therapies. Specifically when used in conjunction with more conventional chemotherapeutics such as doxorubicin, blockade of autophagy-properly targeted such as by ULK1 targeting– holds a great promise for cancer therapy. The observed differences in basal autophagy activity with respect to ULK1 inhibiting doses between various cancer cell lines underline the necessity of indication-specific molecular methods in the construction of efficient therapy plans [25]. The fact that the functions of autophagy are context-dependent and dynamic [that can promote cell survival while under certain genetic and environmental conditions it can lead to cell death 26] adds up to the complication of the potential for therapeutic use of autophagy modulation in cancer. Therefore, the creation of targeted and effective cancer treatments has a strong dependency on improved insight into molecular mechanisms regulating autophagy and their interactions with other processes within the cell [27]. To gain full insight of what ULK1 phosphorylation, particularly at Ser 746 is doing to modulate autophagy under genotoxic stress; in order to explore potential therapeutic benefits of targeting this specific phosphorylation site [28] to better chemosensitivity of cancer cells.

Lysosomal membrane permeabilization is the other key process in autophagy-mediated cell death. thus, using this pathway may contribute to overcome death resistance in cancer cells [27]. The results also demonstrate that the combination of ULK1 inhibitors and chloroquine highly increases cytotoxicity, hence leading to both necrosis and death in cancer cells. Defeating resistance to death is a frequent event in many cancer cells [29] that especially rely on this dual process of cell death. The reported synergistic effect means that the ULK1 inhibition sensitizes the cancer cells to lysosomal stress that is created by chloroquine therefore it eases a more efficient death of the cell

response. These results are compatible with an ever-growing mass of data suggesting that autophagy and death are related processes and that with alteration of both at the same time more effective cancer treatment will be achieved [30]. Further studies describing the interplay between autophagy and metabolism, and stress signaling in cancer cells would be justified by the contrasting responses observed upon inhibition of ULK1 in various cancer cell lines, which could be explained by differences in their metabolic frailties and adaptive stress responses. Moreover, it should be understood that although autophagy inhibition has proved promise in sensitising cancer cells to treatment, its long term effects in the context of cancer development and progression in human beings need to be studied very carefully. In certain tumors, it may be feasible to target SNAREs complex in order to arrest autophagy [5]. Furthermore, autophagy regulates protein degradation, and hence controlling senescence [4]. Patients with osteoarthritis [18] experience dropping autophagy. More, regulating autophagy is the mammalian target of rapamycin (mTOR [31]. As a kind of negative regulator, mTOR decreases the ULK1 complex. Mitochondrial malfunction [19] can be caused by pathological disturbance of nutrient-sensing systems. Every effort to control cell survival will have to be focused at Wnt/β-catenin signaling, PI3K/AKT/mTOR signaling, and MAPK pathway [32].

The several roles of autophagy in the cancer confirm the necessity of indication-specific molecular methods in the design of optimal therapeutic schemes. Cell death in treatment resistance correlates to observations; various forms of malignancies have proven not to initiate apoptosis [33]. Hemostological cancers [34] usually present with increased and uncontrolled kinase activity. Several molecules in the death pathways can be the new and effective approach not only to prevent therapy resistance but also to indicate new anticancer treatments [35].

Conclusion:

Overall, our thorough evaluation of autophagy's role in cancer cells provides evidence that important autophagy markers (LC3-II and p62) display differential expression in A549, MCF-7, HeLa, PC3 and Hct 116 cell lines as a consequence of distinct basal autophagic flux profiles, that are associated with sensitivity or resistance to pharmacologic inhibition. significantly, HeLa cells displayed the highest LC3-II (1.5 AU) but the lowest IC_{50} (1.8 μM) in contrast to HCT116, which is indicative of increased susceptibility of tumours with increased autophagy to ULK1 inhibition. Chloroquine monotherapy in a dose-dependent manner dramatically reduced MCF-7 viability; however, when used in combination with doxorubicin, apoptotic cell death took precedence (75% vs. 25% necrocytosis) underlining the promise that the inhibition of autophagy may enhance the potency of chemotherapeutic agents. Further establishing autophagy as a therapeutic vulnerability, bear strong inverse correlations between LC3-II levels and inhibitor IC_{50} ($r = -0.85$). in vitro A549 viability decreased in a dramatic manner with increasing ULK1 inhibitor concentrations. On the other hand, higher p62 expression was associated with lower inhibitor sensitivity ($r = 0.72$) thus underscores the potential of p62 to be used as a biomarketer for stratifying individuals likely to derive benefit from autophagy targeted therapy. With HeLa derived tumors reducing by 40% while other models reduce by 20–35%, in vivo, ULK1 inhibition had translational value and significantly slowed tumor growth in xenograft models. These combined results demonstrate the ability to modulate context-specific autophagy that is LC3-II and p62 expression guided, to effectively diminish survival of cancer cells, promote death triggered by chemotherapy, and inhibit tumor progression. Future studies should focus on delineating molecular determinants of autophagy dependence across tumor subtypes, refining combination schedules of existing chemo

therapeutics and immunotherapeutics, and testing next generation autophagy inhibitors in clinical trials to fully exploit autophagy inhibition as a precision oncology approach.

References:

1. Thorburn A. Crosstalk between autophagy and apoptosis: Mechanisms and therapeutic implications. Progress in Molecular Biology and Translational Science 2020:55.
2. Tonkin-Reeves A, Giuliani CM, Price JT. Inhibition of autophagy; an opportunity for the treatment of cancer resistance. Frontiers in Cell and Developmental Biology 2023;11.
3. Shliapina VL, Yurtaeva SV, Rubtsova MP, Dontsova OA. At the Crossroads: Mechanisms of Apoptosis and Autophagy in Cell Life and Death. Acta Naturae 2021;13:106.
4. Liu Y, Zhang Z, Li T, Xu H, Zhang H. Senescence in osteoarthritis: from mechanism to potential treatment. Arthritis Research & Therapy 2022;24.
5. Zheng D, Chen S, Cai K, Lei L, Wu C, Sun C, et al. Prodigiosin inhibits cholangiocarcinoma cell proliferation and induces apoptosis via suppressing SNAREs-dependent autophagy. Cancer Cell International 2021;21. https://doi.org/10.1186/s12935-021-02355-3.
6. Jung S, Myagmarjav D, Jo T, Lee S, Han S, Quynh NTN, et al. Inhibitory role of TRIP-Br1 oncoprotein in anticancer drug-mediated programmed cell death via mitophagy activation. International Journal of Biological Sciences 2022;18:3859. https://doi.org/10.7150/ijbs.72138.
7. Kumari R, Ray AG, Mukherjee D, Chander V, Kar D, Kumar US, et al. Downregulation of PTEN Promotes Autophagy via Concurrent Reduction in Apoptosis in Cardiac Hypertrophy in PPAR α−/− Mice. Frontiers in Cardiovascular Medicine 2022;9.
8. Zambrano-Román M, Padilla-Gutiérrez JR, Valle Y, Muñoz-Valle JF, Valdés-Alvarado E. Non-Melanoma Skin Cancer: A Genetic Update and Future Perspectives. Cancers 2022;14:2371.
9. Kaleağasıoğlu F, Ali DM, Berger MR. Multiple Facets of Autophagy and the Emerging Role of Alkylphosphocholines as Autophagy Modulators. Frontiers in Pharmacology 2020;11.
10. Xue Q, Kang R, Klionsky DJ, Tang D, Liu J, Chen X. Copper metabolism in cell death and autophagy. Autophagy 2023;19:2175.
11. Mali SB. Cancer treatment: Role of natural products. Time to have a serious rethink. Oral Oncology Reports 2023;6:100040.
12. Ghosh S, Marrocco I, Yarden Y. Roles for receptor tyrosine kinases in tumor progression and implications for cancer treatment. Advances in Cancer Research 2020:1.
13. Sánchez-León ML, Jiménez-Cortegana C, Cabrera G, Vermeulen EM, Cruz-Merino L de la, Sánchez-Margalet V. The effects of dendritic cell-based vaccines in the tumor microenvironment: Impact on myeloid-derived suppressor cells. Frontiers in Immunology 2022;13.
14. Antona A, Varalda M, Roy K, Favero F, Mazzucco E, Zuccalà M, et al. Dissecting the Mechanism of Action of Spiperone—A Candidate for Drug Repurposing for Colorectal Cancer. Cancers 2022;14:776.
15. Zheng S, Han H, Lin S. N6-methyladenosine (m6A) RNA modification in tumor immunity. Cancer Biology and Medicine 2022;19:385.
16. Krstić J, Pieber TR, Prokesch A. Stratifying nutritional restriction in cancer therapy: Next stop, personalized medicine. International Review of Cell and Molecular Biology 2020:231.
17. Cortellino S, Longo VD. Metabolites and Immune Response in Tumor Microenvironments. Cancers 2023;15:3898.

18. Coryell P, Diekman BO, Loeser RF. Mechanisms and therapeutic implications of cellular senescence in osteoarthritis. Nature Reviews Rheumatology 2020;17:47.
19. Ansari MdM, Ghosh M, Lee D, Son Y. Senolytic therapeutics: An emerging treatment modality for osteoarthritis. Ageing Research Reviews 2024;96:102275.
20. Stine ZE, Schug ZT, Salvino JM, Dang CV. Targeting cancer metabolism in the era of precision oncology. Nature Reviews Drug Discovery 2021;21:141.
21. Zhao H, Li Y. Cancer metabolism and intervention therapy. Molecular Biomedicine 2021;2.
22. Iyikesici MS, Slocum AK, Winters N, Kalamian M, Seyfried TN. Metabolically Supported Chemotherapy for Managing End-Stage Breast Cancer: A Complete and Durable Response. Cureus 2021.
23. [23] Li Y, Tian X, Luo J, Bao T, Wang S, Wu X. Molecular mechanisms of aging and anti-aging strategies. Cell Communication and Signaling 2024;22. https://doi.org/10.1186/s12964-024-01663-1.
24. Karabacak NM, Zheng Y, Dubash TD, Burr R, Micalizzi DS, Wittner BS, et al. Single cell proteomics of tumor compartments identifies differential kinase activities defining sensitivity to mTOR-PI3-kinase inhibition. bioRxiv (Cold Spring Harbor Laboratory) 2021.
25. Banchereau R, Leng N, Zill OA, Sokol ES, Liu G, Pavlick D, et al. Molecular determinants of response to PD-L1 blockade across tumor types. Nature Communications 2021;12.
26. Guilbaud E, Galluzzi L. Adaptation to MOMP drives cancer persistence. Cell Research 2022;33:93.
27. Khan SU, Pathania AS, Wani A, Fatima K, Mintoo MJ, Hamza B, et al. Activation of lysosomal mediated cell death in the course of autophagy by mTORC1 inhibitor. Scientific Reports 2022;12.
28. Torii S, Yamaguchi H, Nakanishi A, Arakawa S, Honda S, Moriwaki K, et al. Identification of a phosphorylation site on Ulk1 required for genotoxic stress-induced alternative autophagy. Nature Communications 2020;11.
29. Wood KC. Overcoming MCL-1-driven adaptive resistance to targeted therapies. Nature Communications 2020;11.
30. Tang M, Hu X, Wang Y, Yao X, Zhang W, Yu C, et al. Ivermectin, a potential anticancer drug derived from an antiparasitic drug. Pharmacological Research 2020;163:105207.
31. Wakale S, Wu X, Sonar Y, Sun AR, Fan X, Crawford R, et al. How are Aging and Osteoarthritis Related? Aging and Disease 2023;14:592.
32. Fu D, Hu Z, Xu X, Dai X, Liu Z. Key signal transduction pathways and crosstalk in cancer: Biological and therapeutic opportunities. Translational Oncology 2022;26:101510.
33. Oliver L, Lalier L, Salaud C, Heymann D, Cartron PF, Vallette FM. Drug resistance in glioblastoma: are persisters the key to therapy? Cancer Drug Resistance 2020.
34. Mologni L, Marzaro G, Redaelli S, Zambon A. Dual Kinase Targeting in Leukemia. Cancers 2021;13:119.
35. Rajabi S, Maresca M, Yumashev AV, Choopani R, Hajimehdipoor H. The Most Competent Plant-Derived Natural Products for Targeting Apoptosis in Cancer Therapy. Biomolecules 2021;11:534.