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Linking Autophagy and the Dysregulated NF κ B/SNAIL/YY1/RKIP/PTEN Loop in Cancer: Therapeutic Implications

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Abstract

The role of autophagy in the pathogenesis of various cancers has been well documented in many reports. Autophagy in cancer cells regulates cell proliferation, viability, invasion, epithelial-to-mesenchymal transition (EMT), metastasis, and responses to chemotherapeutic and immunotherapeutic treatment strategies. These manifestations are the result of various regulatory gene products that govern autophagic, biochemical, and molecular mechanisms. In several human cancer cell models, the presence of a dysregulated circuit—namely, NF κ B/SNAIL/YY1/RKIP/PTEN—that plays a major role in the regulation of tumor cell unique characteristics just listed for autophagy-regulated activities. Accordingly, the autophagic mechanism and the dysregulated circuit in cancer cells share many of the same properties and activities. Thus, it has been hypothesized that there must exist a biochemical/molecular link between the two. The present review describes the link and the association of each gene product of the dysregulated circuit with the autophagic mechanism and delineates the presence of crosstalk. Crosstalk between autophagy and the dysregulated circuit is significant and has important implications in the development of targeted therapies aimed at either autophagy or the dysregulated gene products in cancer cells.

Keywords

Autophagy; NF κ B; PTEN; RKIP; SNAIL; therapy; YY1

I. INTRODUCTION

Among the variety of diseases that affect human kind, cancer remains one of the most prevalent, leading to a large number of deaths. Unlike other microbial diseases, cancer is not a single uniform disease, consisting as it does of a large number of distinct histological, molecular, and genetic types as well as subtypes. For this reason, the pathogenesis of each cancer type is different and requires a fundamental understanding of properties and behaviors in an effort to develop effective targeted treatments. Cancers arise as a consequence of genetic mutations, resulting in the expression of oncogenes, loss of tumor-suppressor genes, activated survival pathways, and so forth. Oncogenes play a pivotal role in abnormal cell growth proliferation, invasion, metastasis, and several mechanisms to evade cytotoxicity by the immune antitumor response and the response to a variety of cytotoxic chemotherapeutic drugs.

Current cancer therapeutic studies have emerged following the initial development of nonspecific cytotoxic chemotherapeutic drugs and subsequently the development of drugs that target survival signaling pathways and tumor-associated cell surface receptors,¹ as well as therapeutic monoclonal antibodies and T-cell-mediated therapeutics.² Recently, significant clinical responses of some cancers were observed through the development of checkpoint inhibitors³ and CAR-T-cell cytotoxic therapies.^{4,5}

It is important to recognize the significant advances made in the treatment of various cancers with the just mentioned modalities, used alone or in combination with various therapeutics, that have resulted in significant clinical responses with longer remissions and fewer recurrences for a large subset of cancer patients. However, encountered and observed in the clinic are the findings that a large percentage of patients do not initially respond to treatments, and that a subset of responding patients become refractory to further treatments and experience relapses and recurrences. Clearly, cancer cells, in striving to survive, develop several molecular, biochemical, and genetic mechanisms to evade cell death. Therefore, the current emphasis is on investigations to unravel the underlying molecular and genetic mechanisms by which tumor cells, or a subset of cancer stem cells, evade cell death, and to delineate several factors that regulate resistance to cell death by most chemo-immuno-therapeutics.⁶

A large number of resistance mechanisms have been explicated, including drug efflux, DNA repair mechanisms, drug metabolism alterations, drug target modifications, cell survival pathway activation, apoptotic pathway dysregulation, gene activation (through epigenetics), recognition of a small subset of cancer stem cells, downregulation of tumor-associated antigenic regions, and the like. In cell-mediated immunotherapy, the expression of inhibitory ligands by resistant tumor cells, such as the upregulation of CTLA-4, PDL1, and PDL2, prevents either the induction of an antitumor response or the inhibition of the cytotoxic effector function of antitumor CTLs.^{6–9}

II. THE DYSREGULATED NF κ B/SNAIL/YY1/RKIP/PTEN LOOP IN VARIOUS CANCERS

Studies examining potential underlying mechanisms of tumor cell resistance have found that, in a large number of cancer cell lines, there exists a closed circuit that controls cell proliferation and viability, invasion, metastasis, and death, as well as regulates tumor cell resistance to both chemotherapeutic drugs and immune-mediated cytotoxic lymphocytes. This dysregulated circuit consists of the NF κ B/SNAIL/YY1/RKIP/PTEN gene products.^{10–13} Brief descriptions of each of these and its relationship to autophagy are provided next.

III. AUTOPHAGY

It is well recognized that inflammation is closely linked to cancer initiation and progression.¹⁴ For instance, microbial infection is sufficient to form some cancers such as cervical and gastric carcinoma.¹⁵ Also, the activation of inflammation-driven signaling pathways modulates the suppression of the antitumor immune response.^{15,16} Of importance is the demonstration that inflammation-mediated signaling pathways promote, in several cancers,

tumor cell evasion and escape from apoptosis; DNA damage; crosstalk with oxidative stress pathways; tumor cell growth, proliferation and viability; metastasis; and resistance to cytotoxic therapeutics.

Autophagy is a conserved lysosomal degradation process in which cells catabolize organelles and proteins in response to starvation and stress. Although the functions of autophagy in tumor cells have been reported to promote cell survival and adaptation to metabolic effects through the recycling of essential metabolites and amino acids, the contrasting functions of autophagy in cancer cells, impeding and promoting tumorigenesis, are now understood.¹⁷ While autophagy's influences on the tumor microenvironment are not completely clear, it is possible that, in the inflammatory response in cancer, they are diverse and triggered by multifaceted pathways.¹⁴

Three autophagic mechanisms have been recognized: macroautophagy, microautophagy, and chaperone-mediated autophagy.¹⁸ Macroautophagy represents the importance of autophagy, and most reports on autophagy mean this mechanism. It is a process in which intracellular compounds are degraded for nutrient recovery through phagophores (isolation membrane), sequestering them into a double membrane in the form of vacuoles (autophagosomes) and fusion with lysosomes (so-called autolysosomes). Microautophagy is a nonselective degradative mechanism that directly engulfs cytoplasmic components or organelles into tubules to the lysosomes.¹⁹ Chaperone-mediated autophagy (CMA) degrades cellular proteins possessing the KFERQ sequence motif, subsequent to recognition by the cytosolic heat shock protein of 70KD (Hsp70). The cellular proteins form a complex with Hsp70 and its chaperone for delivery to the lysosomes, where they interact with the lysosome-associated membrane protein (LAMP) and thereby undergo degradation.²⁰

A. Macroautophagy/Autophagy

Autophagy-related proteins (Atgs) are vital in autophagosome formation. The mechanism of macroautophagy is well understood.^{17,18} The initial step in autophagosome formation is mediated by the complex of ULK-1-Atg13-FIP200. This complex is negatively regulated by the mammalian target of rapamycin (mTOR) through ULK phosphorylation. The second step, phagophore nucleation, is mediated by the Class III phosphatidylinositol 3-kinase (PI3K) Beclin-1 complex, which consists of Beclin-1, Atg14L, Vps15, and Vps34. The third step (elongation) is Atg5-Atg12 formation along with Atg16 to become the Atg5-Atg12-Atg16 complex. Simultaneously, LC3I (Atg8) is cleaved by Atg4 and in turn conjugated with phosphatidyl ethanolamine (PE) by Atg3 and Atg7 to become LC3-II. The double membrane-associated LC3-II is involved in the phagophore enclosure and results in autophagosome formation.¹⁸

Since both the dysregulation of the NF κ B/SNAIL/YY1/RKIP/PTEN loop and autophagy in large part regulate inflammatory and cytotoxic responses, it is justified to presume that the dysregulated loop in cancer cells is also involved in autophagy regulation in cancer and vice versa. In this review, I present the potential linkage of each dysregulated gene product in the loop with autophagy in cancer.

IV. THE LINKAGE OF THE DYSREGULATED LOOP WITH AUTOPHAGY

A. NF κ B versus Autophagy

The transcription factor NF κ B is the dominant regulator of inflammatory response. While many cytokines signal NF κ B transcription, NF κ B-dependent transcription enhances inflammatory responses. The activation of NF κ B results in its translocation into the nucleus and the transcription of many genes. In cancer cells, NF κ B activity results in the inhibition of antitumor immunity, potentiation of tumorigenic inflammation, and tumor cell proliferation and angiogenesis.²¹ NF κ B also interacts with autophagy, leading to alterations in tumor cell survival and apoptosis.

Autophagy modulates NF κ B signaling in the tumor microenvironment (TME) and in tumor cells. In a model of mouse hepatoma cells, autophagy opposes NF κ B activation by degrading RELA/p65 aggregation in tumor-associated macrophages, which results in cytokine IL-6 and IL-12 secretions and an M2 phenotype.²² In addition, several members of the NF κ B-activating signaling pathways interact with the autophagy pathway in cancer cells.^{23,24} More details are provided by Monkkonen and Debnath.¹⁴

NF κ B activation is intrinsically involved in tumor-associated inflammation partly via the transcriptional activation and synthesis of various cytokines that mediate inflammation.¹⁴ This has both inhibiting and enhancing effects on autophagy. For instance, the sustained upregulation of IL6 in lung carcinoma cell lines and their transformation correlate with inhibition. Because IL-6-mediated transformation results from inhibition of the Beclin1-Bcl-2 complex, the overexpression of Beclin-1 blocks IL-6-mediated transformation.²⁵ Also, in melanoma cells the blocking of IL-1 increases autophagy flux and concomitantly inhibits cell growth, suggesting that IL1 inhibits autophagy as well.²⁶ The ablation of IL-6 results in, among many defects, the inhibition of both NF κ B and MAPK8/c-Jun kinase activation.¹⁶ In contrast, the interferon gamma (IFN- γ) cytokine stimulates autophagy during tumorigenesis by upregulating Beclin-1.²⁷

Tumor cell autophagy has an impact in the TME through the recruitment of inflammatory cells and inhibition of both innate and adaptive immunities.^{28,29} It affects antigen cross-presentation in tumors. In melanoma cells, inhibition of autophagy stimulates antigen cross-presentation and inhibits tumorigenesis; in contrast, it decreases antigen uptake and enhances tumorigenesis.³⁰ Tumor cell autophagy may increase antigen cross-presentation and extend survival^{31,32} and increases immunogenic cell death and response to chemotherapy.^{32,33} On the other hand, it reduces natural killer activity and inhibits tumor cell killing.²⁹

The role of autophagy in cancer is context dependent. Its role in cancer cell survival is important. Chloroquine (CQ) is a main autophagy blocker. Its mode of action was investigated by Yang et al.,³⁴ who demonstrated that CQ induces NF κ B activation in human tumor cell lines and subsequently expression of its target genes *HIF-1 α* , *IL-8*, *BCL2*, and *BCLXL* through the accumulation of autophagosomes, p62 and JNK signaling. Gene expression of p62 is increased by NF κ B activation. The inhibition of NF κ B or knockdown of p62 sensitizes tumor cells to CQ and leads to increased apoptotic cell death. Two human

pancreatic carcinoma cell lines were used in the Yang et al. study. Treatment with inhibitors for either MAPK or NF κ B resulted in the inhibition of cell growth. In the presence of autophagy inhibitors, apoptosis was observed.

The complex role of NF κ B and autophagy remains an important area of research. Clearly, NF κ B signaling can regulate autophagy and autophagy can alter NF κ B signaling. Nevertheless, crosstalk exists between NF κ B and autophagy in both directions (Fig. 1.)

B. SNAIL versus Autophagy

In the dysregulated loop, the inhibition of NF κ B results in the downstream inhibition of YY1 and SNAIL and the upregulation of RKIP, leading to tumor cell sensitization to both chemo- and immune-mediated apoptosis.^{35–39}

SNAIL is a transcription factor that belongs to the SNAIL superfamily of zinc finger transcription factors. It is involved in embryonic development, neural differentiation, cell division, survival, invasion, EMT, and metastasis.^{40,41} SNAIL is transcriptionally regulated by both NF κ B⁴² and YY1.⁴³ It represses the transcription of E-cadherin⁴⁴ and RKIP,⁴⁵ and is intrinsically involved in EMT via suppression of E-cadherin. The relationship between SNAIL-induced EMT and autophagy was investigated by Grassi et al.,⁴⁶ who examined the nontumorigenic immortalized hepatocyte cell line MH in a liver-specific autophagy deficiency in mice. They found that the level of SNAIL increases post-transcriptionally. Autophagy degrades SNAIL but its inhibition increases SNAIL. Therefore, stimulation of autophagy inhibits EMT progression (Fig. 2).

Catalano et al.⁴⁷ reported that autophagy is induced in glioblastoma cells by nutrient deprivation or by a pharmacological inhibitor. Both impairments of migration and invasiveness were observed. These were the results, in part, of the downregulation of SNAIL and SLUG, the regulation of EMT, and the upregulation of N- and R-cadherins. Thus, autophagy induction triggers a switch from the mesenchymal phenotype to an epithelial phenotype.

In contrast to the role of autophagy in the induction and inhibition of EMT via SNAIL degradation, studies by Lu et al.⁴⁸ reported that miR517c expression is associated with good prognosis of glioblastoma (GBM). MiR57c inhibits autophagy and inhibits cell migration and infiltration. Further, expression of the epithelial markers E-cadherin and Claudins increase, whereas expression of the mesenchymal markers N-Cadherin, SNAIL, and vimentin decrease, demonstrating that EMT is blocked by miR517c.

C. RKIP

The RAF kinase inhibitory protein (RKIP) is a member of the phosphatidyl ethanolamine-binding protein family that has been reported to have a role in lipid metabolism and phospholipid membrane biogenesis.⁴⁹ Yeung and associates were the first to clone RKIP and demonstrate the inhibitory effects of the RAF/MAPK/ERK and NF κ B pathways.^{50,51} RKIP negatively regulates the activation of G-protein-coupled receptors (GPCRs).⁵² RKIP has been reported to be a metastasis suppressor⁵³ and to regulate metastasis by the inhibition of MMP.⁵⁴ It has also been shown to regulate drugs/immune resistance and the cancer stem cell

phenotype.¹⁰ RKIP can be phosphorylated at serine-153, leading to its inhibitory effects on the RAF/MAPK/ERK and NFκB signaling pathways.⁵⁵

RKIP expression is downregulated in the majority of cancers. Wen et al.⁵⁶ demonstrated that RKIP is a substrate of the cyclin-dependent kinase 5 (CDK5) in neurons and that its phosphorylation at S42 releases it from RAF. Furthermore, T42 phosphorylation of RKIP exposes the motif between “KLYEK” in its C terminus and is targeted by chaperone Hsp70, resulting in RKIP degradation via chaperone-mediated autophagy.

RKIP is a negative regulator of autophagy.⁵⁷ The microtubule-associated protein 1 Lightchain 3-B, MAP1LC3B, LC3B, is conjugated with phosphatidyl ethanolamine in the membrane and regulates the initiation of autophagy through interaction with much autophagy-related protein processing and LC3-interacting regions (LIR motif).²⁶ Noh et al.⁵⁷ reported a new putative LIR motif in RKIP. RKIP is specifically bound to phosphatidylethanolamine (PE-) unconjugated LC3 in cells. The overexpression of RKIP inhibits autophagy under starvation conditions. The ablation of RKIP expression promotes it. The phosphorylation of RKIP at serine-153 causes its dissociation from the RKIP-LC3 complex for autophagy induction. Of interest, RKIP-mediated suppression of autophagy is not associated with the MAPK pathway.

In conclusion, RKIP acts as a negative mediator of autophagy through the stimulation of the AKT/mTOR-C1 pathway and its direct interaction with LC3 (Fig. 3)

D. PTEN

The phosphatase and tensin homolog on chromosome 10 (PTEN) is a tumor suppressor, and its expression is low in the majority of cancers. In the dysregulated loop, PTEN expression is low, as it is repressed, in part, by YY1 and therefore enables the AKT/PI3K pathway to be activated and contribute to tumor cell survival, growth, and resistance.

Several studies have examined the relationship between PTEN and autophagy in many different model systems. De Amicis et al.⁵⁸ reported that progesterone in breast cancer cells triggers its receptor PR-B and induces the expression of PTEN (mRNA and protein) and its activation. PR-B binds to an Sp1-rich region on the PTEN promoter through a complex of PR-B and Sp1 and transcriptional co-activators such as SRC1 and CBP. The induction of PTEN results in the downregulation of the PI3K/AKT pathway, turning on autophagy and leading to reduced cell survival. De Amicis et al.⁵⁹ also reported that bergapten (5-methoxypsoralen) treatment of breast cancer cell lines induces autophagy by increasing Beclin-1, PI3K-III, UVRAG, and AMBRA expression and conversion of LC3-I into LC3-II. The induction of autophagy is dependent on PTEN upregulation. Bergapten induction of PTEN is via the P38 MAPK/NF-Y axis. Overall, it has been demonstrated that PTEN is involved in the induction of autophagy.

In the dysregulated loop, the downregulation of PTEN results in the activation of both the AKT/PI3K and NFκB prosurvival pathways, and in the induction of resistance for both chemo- and immunotherapies. A study by Ning et al.⁶⁰ examined the role of PTEN loss in the resistance of breast cancer cells to trastuzumab (anti-HER2 monoclonal antibody.)

Knocking down PTEN and LC3-I/II in HER2-positive breast cancer cells and treatments with trastuzumab results in the inhibition of autophagy. In addition, knockdown of PTEN increases resistance to trastuzumab. There is significant inhibition of the autophagic proteins LC3-I/II, LAMP, p-62, cathepsin-B, and PI3K-AKT-MTOR as well as the signaling pathway mediated by AKT. All have been observed compared to PTEN control following treatment with trastuzumab. Thus, the loss of PTEN promotes the development of resistance to trastuzumab via defects in autophagy. This finding corroborates the role of low PTEN in the loop and immune resistance (Fig. 4).

MiR-21 expression suppresses autophagy through the AKT/PTEN pathway and correlates with the resistance to drugs like sorafenib in hepatocellular carcinoma cells⁶¹ and resistance to tamoxifen and fulvestrant in breast cancer cells.⁶² Knockdown of miR-21 in breast cancer cells increases apoptosis mediated by tamoxifen and fulvestrant and enhances cell autophagy; it also induces increases in Beclin-1 and LC3-II and contributes to autophagic cell death through the inhibition of the PI3K-AKT-MTOR pathway by targeting PTEN.

The role of PTEN in the induction and regulation of autophagy can be mediated by its slow expression or degradation, or by S-nitrosylation. Zhu et al.⁶³ reported that NOS-1 inhibits autophagy and promotes survival of nasal pharyngeal cancer cells. The role of NOS-1 in autophagy is via the activation of the AKTMTOR pathway by s-nitrosylation of PTEN.

E. YY1

The transcription factor YY1 is a member of the GLI-Kruppel class of zinc finger proteins. It plays several roles in many biological processes. YY1 can either activate or suppress gene expression depending on its interactions and contexts, and it also functions as a master of the epigenetic network.^{64,65} The expression of YY1 is upregulated in many cancers and plays an important role in cancer development.^{66,67} Bonavida and Beritaki reported that YY1 regulates EMT, cell survival, and resistance to both chemo- and immunotherapies.¹⁰ It can also modulate skeletal muscle differentiation by silencing the expression of a series of miRNAs.^{48,68}

Autophagy is implicated in carcinogenesis. It can act as a tumor suppressor, such that Beclin-1 has been found to be the first gene product to function in both cancer and autophagy.^{69,70} Autophagy-deficient T-cells are more tumorigenic than autophagy-competent T-cells.^{71,72} In contrast, autophagy is protumorigenic. For instance, blocking autophagy enhances the apoptosis induced by various chemotherapeutic drugs.⁷³ Also, the accumulation of SQSTM1/p-62 promotes tumorigenesis and its inhibition results in the inhibition of tumor growth in mice.^{72,74}

YY1 promotes autophagy and promotes tumor growth through the inhibition of miR-372, whose target is SQSTM1. Inhibition of autophagy potentiates drug sensitivity. The role of YY1 in the autophagy of pancreatic cancer was reported by Yang et al.³⁴ YY1 directly targets miR-30a, whose targets are Atg-5 and Beclin-1.^{75,76} In turn, miR-30a regulates the expression of YY1, suggesting a YY1/miR-30a regulating circuit that controls autophagy in pancreatic cancer. YY1 promotes autophagy by suppressing miR-30a, by which it modulates the autophagy-associated genes *Atg-5* and *Beclin-1*. Also, YY1 is targeted by miR-30a via a

negative feedback loop. Interestingly, in pancreatic cancer it promotes apoptosis and plays a tumor-suppressive role.⁷⁷ YY1 promotes autophagy and attenuates pancreatic cancer growth. (Fig. 5)

V. DISCUSSION

This review extrapolated from the literature a close linkage between autophagic mechanisms and the gene products of the dysregulated NF κ B/SNAIL/YY1/RKIP/PTEN circuit in cancer cells. Not all autophagic mechanisms in cancer cells are identical but rather play contrasting roles in different cancer cells and/or in the same cancers under different conditions. Clearly, the studies reported here illustrate the complexity of the autophagic process and its potential underlying mechanisms that regulate cell survival and escape from cell death. Their findings concur with those of similar studies on the role of each gene product involved in the dysregulated loop.

Each gene product of the dysregulated loop and its relationship with autophagy were examined here. For instance, it was found that autophagy modulates the NF κ B pathway in cancer cells, and that several markers of the pathway interact with autophagy.^{14,22,24} The NF κ B signaling pathway is intrinsically involved in the transcription and regulation of various inflammatory cytokines that have also been shown to regulate autophagy (either inhibition or activation). Clearly, NF κ B signaling regulates autophagy and autophagy regulates NF κ B signaling.³⁴ A clear association between SNAIL and autophagy in EMT has been reported.⁴⁶ Autophagy plays a role in the degradation of SNAIL and triggers a switch from the mesenchymal to the epithelial type, a phenomenon observed in metastatic tumors.⁴⁷ In contrast, Liu et al.¹⁷ reported that the inhibition of autophagy results in the inhibition of cell migration and invasion as well as the reversal of the EMT phenotype to an MET phenotype through the downregulation of N-cadherin, SNAIL, and vimentin.

The low expression of RKIP in many cancers has been reported, and it has been shown that RKIP expression mediates tumor-suppressive activity and inhibits EMT, as well as sensitizes tumor cells through cytotoxic therapies.¹⁰ It has also been reported that RKIP is a negative regulator of autophagy⁵⁷ and inhibits tumor cell characteristics, thus establishing a direct negative association between RKIP and autophagy. The low expression of PTEN in cancer cells results in failure to inhibit the hormonal-resistant PI3K/AKT pathway in cancer cells. Paradoxically, PTEN is involved in the induction of autophagy^{58,59} and its loss promotes tumor cell resistance to cytotoxic therapies. The transcription factor YY1 is reported to promote autophagy and tumor growth as well as resistance to cytotoxic drugs. There is dual regulation between YY1 and autophagy gene products such as Atg-5 and Beclin-1 and vice versa.^{34,77}

Drugs that induce DNA damage (e.g., cisplatin and temozolomide) and inhibit DNA synthesis (e.g., 5-Fu and gemcitabine), along with HDAC inhibitors (e.g., SAHA), induce growth inhibition and autophagy in order to survive. Other agents that target signal transduction pathways (e.g., erlotinib and gefitinib); the tyrosine kinase inhibitor imatinib, BRAF mutation inhibitors vemorafenib and dabrafenib; and the antibody for HER2 amplification trastuzumab) give rise to autophagy and mediate cell survival.^{18,78–82}

Autophagy induction by drugs protects cells from cell death and contributes to acquired resistance.

The autophagosome plays a crucial role in diffusion of endogenous and exogenous antigens with MHC-I/II for potentiation of recognition by T-cell receptors. Hypoxia-induced autophagy results in resistance to T-cell cytotoxicity as a result of STAT3 activation. Hence, inhibition of autophagy by silencing Beclin-1 or Atg-5 correlates with decreased hypoxia-induced activation of STAT3 and lung cancer cells became sensitive to T-cell cytotoxicity. Also, the induction of autophagy facilitates antitumor immunity.³³ Autophagy is a tumor-suppressive mechanism that suppresses tumor-promoting inflammation and the activation of antitumor immunity. The combination of autophagy enhancers with chemo- and immunotherapeutics may augment the efficacy of antitumor immunity.⁸³

Contrasting findings demonstrate the relationship between autophagy suppression and antitumor immune response. Autophagy contributes to malignancy and resistance. The choroquines (chloroquine, CQ and hydroxychloroquine, HCQ) are the only FDA-approved drugs to inhibit autophagy. The clinical effects, however, are modest. A new modified HCQ water-soluble compound, ROC-325, contains HCl and a lucanthone structural motif. Preclinical findings are that ROC-325 exhibits superior lysosomal autophagic inhibition and approximately tenfold more activity against a broad range of tumor cell lines.⁸⁴

VI. CONCLUSIONS

Current findings illustrate the close association of many autophagic mechanisms with those of the gene products of the dysregulated loop. A significant linkage was observed between each dysregulated gene product and autophagy, raising the need to explore these associations and whether autophagy precedes the development of the dysregulated loop or vice versa. Such a possibility has yet to be investigated, and future research in this area is potentially significant for its therapeutic implications.

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ABBREVIATIONS:

CQ	chloroquine
EMT	epithelial-to-mesenchymal transition
PTEN	phosphatase and tensin homolog
RKIP	Raf kinase inhibitor protein
SNAIL	SNAIL

TME tumor microenvironment
YY1 Ying Yang 1

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FIG. 1:

Relationship between NFκB and autophagy. The majority of cancer cells express a constitutively activated NFκB pathway responsible for tumor cell survival, growth, invasion, and resistance to cytotoxic therapies. There exists crosstalk between the NFκB pathway and autophagy. Activated NFκB signals two downstream target gene products, SNAIL and YY1, leading to their overexpression. The overexpression of YY1 negatively regulates miR30A, resulting in the de-repression of both Atg5 and Beclin-1, and thus, leading to the induction of autophagy. Likewise, the overexpression of SNAIL results in the repression of E-cadherin and the induction of EMT. There is crosstalk in both directions between EMT and autophagy (depending on the type of cancer and its properties). The overexpression of SNAIL represses RKIP and leads to its failure to inhibit NFκB (solid lines). If NFκB is inhibited, all of the just described processes are reversed (dashed lines).

FIG. 2:

Relationship between SNAIL and autophagy. In the majority of cancer cells, SNAIL is overexpressed, in part as a consequence of the hyperactivation of NFκB and the overexpression of YY1 that also regulates SNAIL transcription and expression. Overexpression of SNAIL represses E-cadherin, resulting in the induction of EMT. A reversible crosstalk exists between EMT and autophagy (both positively and negatively depending on tumor type and properties). Also, overexpression of SNAIL represses RKIP, resulting in its failure to inhibit NFκB activity. Overexpression of SNAIL, as a result of overexpression of YY1, also regulates autophagy through repression of miR30A, resulting in the de-repression of Atg5 and Beclin-1 and the induction of autophagy (solid lines). If SNAIL expression is inhibited, in part because of the inhibition of NFκB and YY1, the processes described above for the overexpression of SNAIL are reversed (dashed lines)

FIG. 3:

Relationship between downregulation of RKIP and autophagy. In the majority of human cancer tissues, the expression of the metastasis repressor RKIP is downregulated, in part as a result of the hyperactivation of NFκB and the RKIP repressor SNAIL. RKIP downregulation maintains the hyperactivation of NFκB and its downstream target, overexpressed YY1. The overexpression of YY1 results in the inhibition of miR30A, which then results in the up-regulation of Atg5 and Beclin-1, leading to autophagy (solid lines). In contrast, the overexpression of RKIP inhibits, in part, NFκB activity and its downstream targets SNAIL and YY1. The inhibition of SNAIL also de-represses the transcription and expression of RKIP. The inhibition of YY1 activates miR30A, resulting in the inhibition of Atg5 and Beclin-1 and in the absence of autophagy (dashed lines).

FIG. 4:

Relationship between the downregulation of PTEN and autophagy. In most cancer cells, the expression of PTEN is either downregulated or absent. PTEN downregulation is the result, in part, of the hyperactivation of NFκB and the downstream overexpression of the PTEN repressor YY1. The inhibition of PTEN results in the failure to inhibit the PI3K/AKT pathway and in the activation of Beclin-1 and the induction of autophagy (solid lines). In contrast, the overexpression of PTEN, as a result of the inhibition of NFκB activity and the PTEN repressor target YY1, results in inhibition of the PI3K/AKT pathway, inhibition of Beclin-1, and failure to induce autophagy (dashed lines).

FIG. 5:

Relationship between the overexpression of YY1 and autophagy. In the majority of human tissues, YY1 is overexpressed, in part because of hyperactivation of NFκB. The overexpression of YY1 has several manifestations: (1) overexpression of SNAIL, inhibition of E-cadherin, and induction of EMT and crosstalk with autophagy; (2) inhibition of PTEN and maintaining activation of the P13K/AKT pathway, resulting in autophagy; and (3) inhibition of miR30A, leading to expression of Atg5 and Beclin-1 and to autophagy (solid lines). The downregulation of YY1 expression results in processes opposite to those leading to YY1 overexpression (dashed lines).