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CONTENT

MACROAUTOPHAGY AND MITOPHAGY RELATED GENES AFFECT THE SURVIVAL OF ADRENOCORTICAL CARCINOMA PATIENTS
ADRENOKORTIKAL KARSINOM HASTALARININ SAĞKALIMINA ETKI EDEN MAKROOTOFAJI VE MITOFAJI İLIŞKILI GENLER

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ABSTRACT
Introduction: Autophagy has roles in cancer and targeting autophagy at gene level may be promising in a rarely observed adrenocortical carcinoma (ACC) treatment. The aim of the study is to identify prognosis-related autophagy-related genes (ARGs) in ACC patients.
Materials and Methods: Data of 43 ACC patients between 2008-2019 were included. The data and gene intensity values of 222 ARGs for these patients were obtained from the GEO database and the Affymetrix Human Genome U133 Plus 2.0 Array platform. Kaplan Meier method and multivariate Cox regression were used. A useful web-based tool GOrilla (**G**ene **O**ntology en**RI**chmentana**L**ysis and visua**L**iz**A**tion) was used with the two list to clarify the biological relevance. Statistical significance was accepted as p-values <0.05.
Results: The mean age of 43 ACC patients included in the study was 43.3 ± 17.16 (5-77 age range). 67% of the cases were women. Overall survival (OS) was found to be 2.69 ± 3.38 years in multivariate cox regression analysis. It was found that 72% of the patients (31 patients) passed away. Totally, 73 ARGs out of 222 were found to significantly affect the prognosis of patients with ACC. It was shown that 31 of these ARGs had HR value above 1 (hazardous ARGs), while 42 of them had HR value below 1 (survival triggering ARGs). According to GOrilla results, ARGs that significantly affect survival in ACC, which is rare cancer, belong to macroautophagy and mitophagy pathways.
Discussion: Although there are current studies indicating the importance of autophagy in ACC, which is one of the rare cancers, the number of studies focusing especially on mitochondrial processes is limited. Therefore, identification of prognosis related ARGs associated with both macroautophagy and mitophagy can lead to personalized and efficient cancer treatment in a rare cancer of ACC.
Keywords: adrenocortical carcinoma, survival, cancer, autophagy-related genes, macroautophagy, mitophagy

ÖZET
Giriş: Otofajinin kanserde rolü olduğu gösterilmiştirve otofajiyi gen düzeyinde hedeflemek, nadir görülen bir adrenokortikal karsinom (ACC) tedavisinde umut verici olabilir. Çalışmamızın amacı, otofaji ve otofaji-ilişkili genlerin (ARG'ler) ACC hastalarının sağkalımı üzerindeki rolünü araştırmak ve prognozla ilişkili otofaji-ilişkili genleri belirlemektir.
Gereç ve Yöntem: 2008-2019 yılları arasında 43 ACC hastasının verileri dahil edilmiştir. Bu hastalar için 222 ARG'nin verileri ve gen yoğunluğu değerleri, GEO veri tabanından ve Affymetrix Human Genome U133 Plus 2.0 Array platformundan elde edilmiştir. İstatistiksel analiz için Kaplan Meier yöntemi ve çok değişkenli Cox regresyonu kullanılmıştır. Biyolojik anlamlılığı vurgulamak ve açıklığa kavuşturmak için web tabanlı bir araç olan GOrilla (Gene Ontology enRIchmentanaLysis ve visuaLizAtion) kullanılmıştır. İstatistiksel anlamlılık p değeri <0,05 olarak kabul edilmiştir.

Sonuçlar: Çalışmaya dahil edilen 43 ACC hastasının yaş ortalaması 43,3 ± 17,16 (5-77 yaş aralığı)olarak belirtilmiştir. Vakaların% 67'si kadındır. Çok değişkenli cox regresyon analizinde genel sağkalım (OS) 2,69 ± 3,38 yıl olarak bulunmuştur. Hastaların% 72'sinin (31 hasta) vefat ettiği tespit edilmiştir. Toplamda 222 ARG'nin 73 tanesinin ACC'li hastaların prognozunu önemli ölçüde etkilediği bulunmuştur. Bu ARG'lerin 31'inin Hazard Ratio (HR) değerinin 1'in üzerinde olduğu (tehlikeli ARG'ler), 42'sinin ise HR değerinin 1'in altında olduğu (hayatta kalmayı tetikleyen ARG'ler) gösterilmiştir. GOrilla sonuçlarına göre, nadir görülen bir kanser olan ACC'de sağkalımı önemli ölçüde etkileyen ARG'ler, makrootofaji ve mitofaji yolaklarına aittir.
Tartışma: Nadir görülen kanserlerden biri olan ACC'de otofajinin önemini gösteren güncel çalışmalar olsa da özellikle mitokondriyel süreçleri hedef alan çalışma sayısı sınırlıdır. Bu nedenle, hem makrootofaji hem de mitofaji ile ilişkili prognozla ilişkili ARG'lerin belirlenmesi, nadir görülen bir ACC kanserinde kişiselleştirilmiş ve etkili kanser tedavisine yol açabilir.
Anahtar Kelimeler: adrenokortikal karsinom, sağkalım, kanser, otofajiye bağlı genler, makrootofaji, mitofaji

INTRODUCTION

Adrenocortical carcinoma (ACC) is a rare and aggressive cancer with a poor prognosis. Studies have shown that it is seen in 0.7 - 2 cases in a million population annually (Wooten MD. et al 1993, Kebebew E. et al 2006, Rosella Libe 2015). It has been reported that %10-20 of the patients' survival averagely 5 years upon diagnosis (Xiao H. et al, 2018).

Autophagy is a catabolic and self-digestive process in all eukaryotes. It maintains cellular homeostasis by degrading damaged, aging, or denaturing proteins and aged intracellular components to promote nutrient cycling and metabolic adaptation (Levine B, 2004). As a multi-step lysosomal degradation process, autophagy has dual roles in pathological conditions including cancers (Yang ZJ. 2011). For instance, existing studies have shown that autophagy suppresses the cancer cell formation during the early stages of cancer formation by discarding damaged and potential hazardous components inside the cell (White E. 2010). However, autophagy can also promote the growth of cancer cells that are already formed by providing them an adaptation to stress conditions (Degenhardt K 2006). Since the role of autophagy in cancers differs according to the different stages of cancer formation, various studies show that targeting autophagy at gene level has promising effects to eradicate cancers (Amaravadi RK. 2011, Levy JMM. 2017).

There are current studies indicating the importance of autophagy in ACC, which is one of the rare cancers. Studies have generally emphasized the relationship between anticancer chemical agents and endoplasmic-reticulum stress and autophagy, and they mentioned that some agents target mitochondrial functions (Kenneth T., et al 2019, Yunhui C. et al 2016). However, according to our knowledge, macroautophagy and especially microautophagy related genes and their effect on survival has not yet been investigated. Therefore, our study aimed to investigate the role of autophagy and autophagy-related genes (ARGs) on the survival of ACC patients and to identify autophagy related genes associated with prognosis.

MATERIALS AND METHODS

Data Acquisition and Data Processing: A total of 43 patients diagnosed with ACC between 2008 and 2019 were included in this study. Information on the demographic characteristics of the patients and microarray expression profiles were obtained from the Gene Expression Omnibus (GEO) database (ncbi.nlm.nih.gov/geo/). The data were accessed using accession number GSE10927 and GSE33371 (Marisa L. et al.). Age, gender, follow-up time and survival time (OS) of the patients were recorded from this database. In addition, cDNA Microarray data of autophagy-related genes (ARG), a total of 222, were obtained using the human autophagy database (HADb; autophagy.lu/). Gene intensity values of 222 ARGs (MAS5 log2 normalized intensity values of the genes) for ACC

patients were obtained from the [HG-U133_Plus_2] Affymetrix Human Genome U133 Plus 2.0 Array (GPL570) platform containing 54,675 probes (Affymetrix; Thermo Fisher Scientific, Inc). A useful web-based tool Gorilla (Gene Ontology enRIchmentanaLysis and visuaLizAtion tool; http://cbl-gorilla.cs.technion.ac.il/) was used with the two list to clarify the biological relevance of survival-related ARGs. Background genes were accepted as 2581 cancer related genes obtained from http://www.bushmanlab.org/links/genelists. Statistical significance was accepted as p-values <0.05.

Statistical Analysis: Descriptive statistics of variables such as mean and standard deviation are provided. In this study, survival analysis of the patients was analyzed with multivariate Cox regression method with the help of R3.53 programming language and Kaplan Meier graphics were created. R software "Survival" package (version 3.5.1; https://CRAN.R-project. Org / package = survival) was used to perform the survival analysis. Kaplan Meier and Cox Regression analysis were performed.

Ethics Committee Approval: Ethics committee approval was not necessary in this study because publicly open information from the Gene Expression Omnibus (GEO) database was used.

RESULTS

Kaplan Meier and Multivariate Cox Regression Analysis Results in Patients Diagnosed with Adrenocortical Cancer: Sociodemographic data of the patients are given in Table 1. 43 ACC patients are included in the study. 67% of the cases are women. The mean age of the patients is 43.3 ± 17.16 (5-77 age range). Overall survival (OS) is found to be 2.69 ± 3.38 years in multivariate cox regression analysis. It is found that 72% of the patients (31 patients) passed away.

Table 1: Demographic Characteristics of Data

Parameters (n: 43)	n (%)	Mean±SD
Age (years)		43.3 ±17.16
Gender **Male** **Female**	 14 (%33) 29 (%67)	
Survival Time (Years)		2.69±3.38
Survival **Death** **Alive**	 31 (%72) 12 (%28)	

In our study, 73 ARGs out of 222 that significantly affect the prognosis of patients with ACC (n: 43). While the HR value of 31 of these ARGs is above 1 (hazardous ARGs), the HR value of 42 of these ARGs is below 1 (survival triggering ARGs) (Table 2). In addition, Kaplan Meier and survival plots representing the most hazardous and most survival-triggering 3 ARGs are shown in Figure 1 and Figure 2. Our results emphasize the importance of targeting autophagy and related genes for treatment in ACC, a rare cancer type.

Table 2: Multivariate Cox Regression Results, Prognosis Related Significant ARG genes (p-value<0.05)

Gene ID	Hazard Ratio	P-Value	Gene ID	Hazard Ratio	P-Value	Gene ID	Hazard Ratio	P-Value

PELP1	3677,74652***	0,00002	*SPHK1*	7,070041**	0,0296	*MAP1LC3A*	0,046997*	0,0201
MTOR	1857,95551***	0,000522	*PEA15*	5,925644**	0,0481	*ATG101*	0,044516*	0,0099
CAPN10	1444***	0,00241	*MYC*	5,29984**	0,0151	*EEF2K*	0,04041**	0,00107
PEX14	971,56373***	0,00175	*FKBP1B*	5,133622***	0,00129	*ATG4D*	0,036101*	0,0168
GNAI3	520,61227***	4,51E-05	*BIRC5*	3,502786**	0,0233	*SQSTM1*	0,034741*	0,0159
ULK2	260,765797***	0,00979	*PRKCQ*	3,029236**	0,0421	*CDKN1B*	0,03066**	0,00376
ATIC	81,81373***	0,00523	*HSPB8*	0,19999***	1,21E-06	*PINK1*	0,025666*	4,06E-05
IL24	75,165306**	0,0436	*MAPK9*	0,161272***	0,00462	*RB1CC1*	0,023645*	0,0193
ATG4B	65,646852**	0,0138	*IKBKB*	0,157994**	0,0426	*FADD*	0,02277**	0,0027
MAPK1	63,28678***	0,00389	*BAG3*	0,13816**	0,0329	*HSPA8*	0,02233**	0,0465
PARP1	54,213469***	0,00911	*LAMP2*	0,126062**	0,0135	*TNFSF10*	0,021812*	0,000288
WDR45L	44,701***	0,0028	*NRG2*	0,12488**	0,0308	*WDR45*	0,020899*	0,000154
KLHL24	43,79653***	0,00209	*GABARAPL1*	0,09013***	0,000879	*MTMR14*	0,016804*	0,0086
UVRAG	43,35946**	0,0173	*RHEB*	0,08262***	0,00433	*CHMP4B*	0,015632*	0,000286
EIF2S1	30,6469**	0,0208	*CTSD*	0,07789***	0,00216	*GABARAPL2*	0,012559*	0,0068
CD46	27,803816**	0,0263	*MLST8*	0,076124**	0,0169	*ARSB*	0,010677*	0,0126
KIF5B	19,93431**	0,0101	*CTSL1*	0,073358**	0,0485	*DNAJB9*	0,009684*	1,12E-05
ATG9A	16,92785**	0,0415	*CLN3*	0,071516***	0,00301	*ATG4A*	0,007728*	0,000307
FOXO3	13,6169966**	0,0499	*ATG4C*	0,064019***	0,00967	*GRID1*	0,005799*	0,000626
ERBB2	13,559349***	0,00161	*BAG1*	0,06097**	0,0139	*ATF6*	0,005269*	0,00176
RAF1	13,365297**	0,0312	*CANX*	0,057906**	0,0273	*IRGM*	0,005141*	0,00492
ARNT	10,8474765**	0,0431	*VAMP7*	0,056069**	0,0138	*GABARAP*	0,000545*	0,0109
CAMKK2	10,198271***	0,00619	*BNIP1*	0,05233***	0,00161	*RAC1*	0,000165*	0,0273
ATF4	9,3634**	0,0479	*MBTPS2*	0,051565**	0,0323	*PARK2*	0,000131*	6,24E-05
ERO1A	7,683619***	0,00853						

Figure 1: Most Hazardous ARGs that are Statistically Influencing Survival in ACC Patients
Green group represent the patients having the gene intensity lower than average whereas red group represent the patients having gene intensity higher than patients' average.

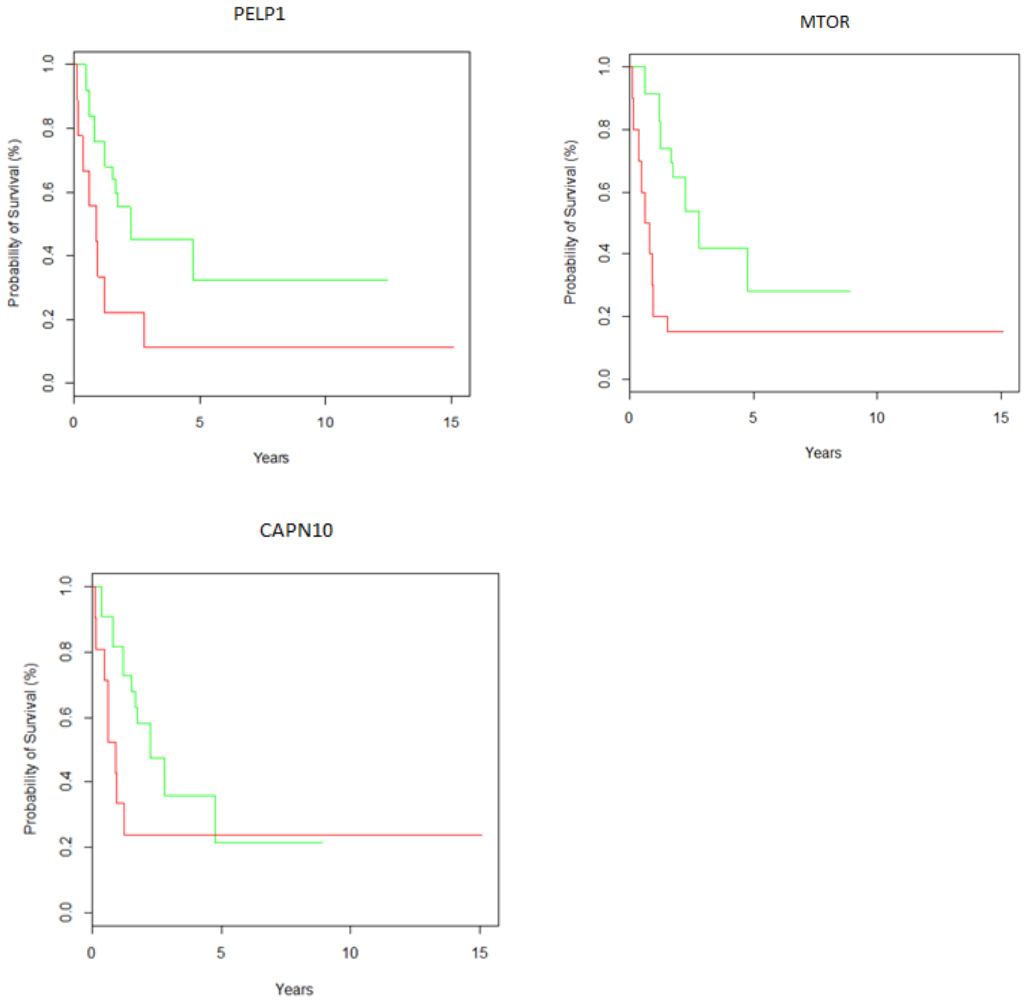
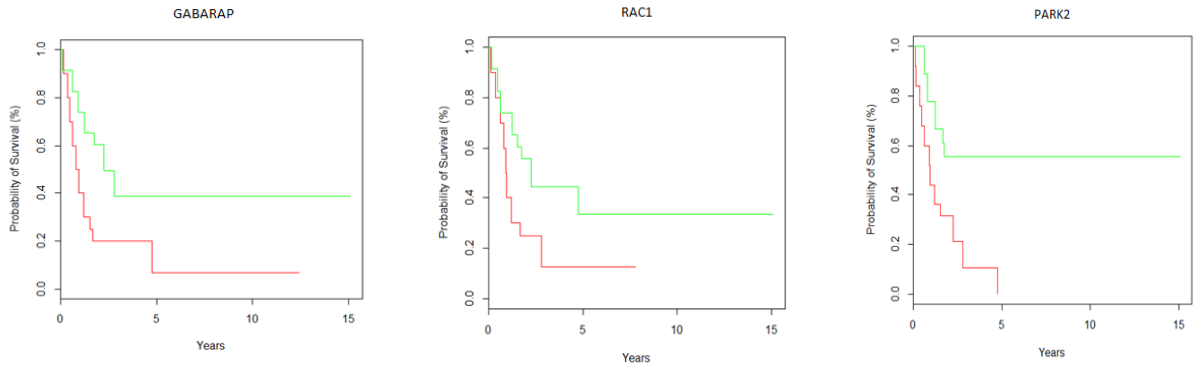
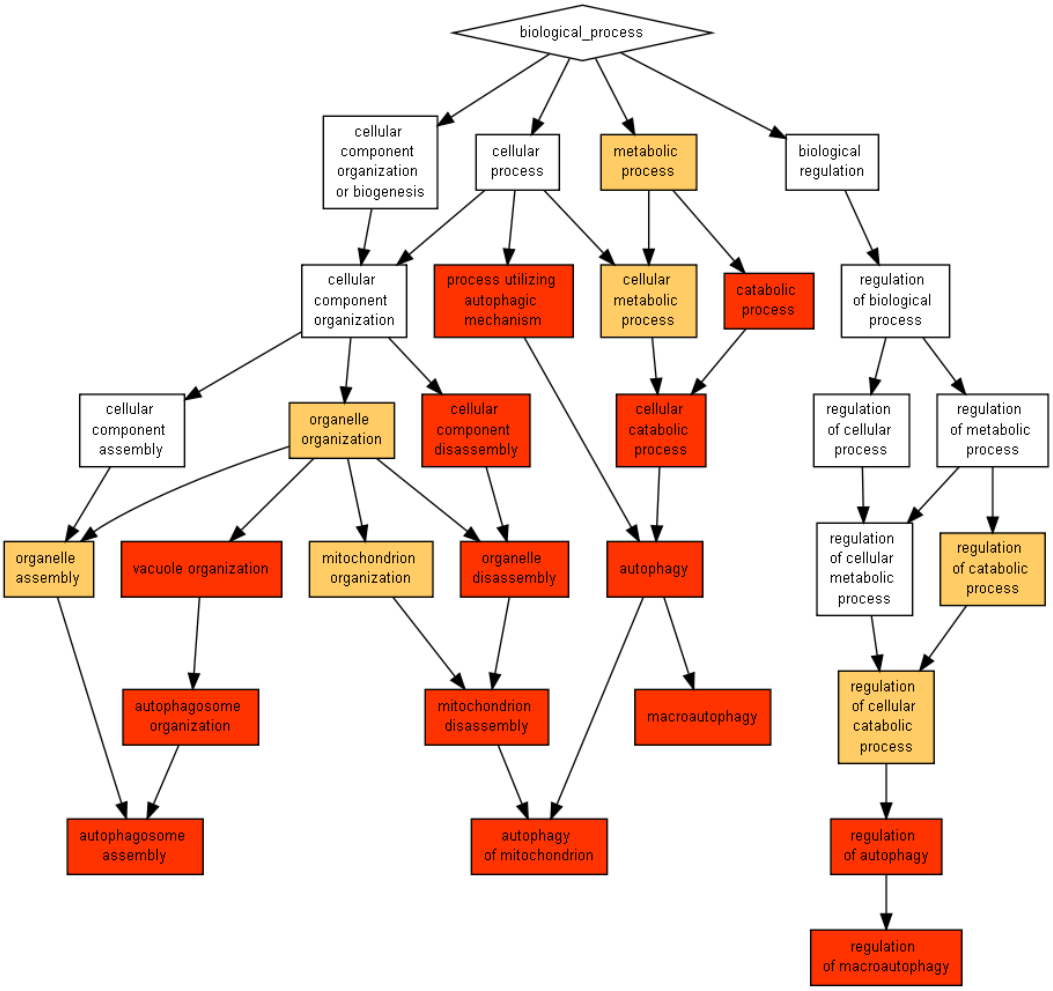


Figure 2: Most Survival Triggering ARGs that are Statistically Influencing Survival in ACC Patients Green group represent the patients having the gene intensity higher than average whereas red group represent the patients having gene intensity lower than patients' average.



Functional Gene Ontology (GO) Enrichment Analysis: A functional gene enrichment analysis was performed to determine the biological significance of the study. As shown in Figure 3, ARGs that significantly affect survival in ACC, which is rare cancer, have been shown to belong to macroautophagy and mitophagy pathways.

Figure 3. Enrichment Gorilla Analyses Point out Both Macroautophagy and Mitophagy as a Target Treatment Pathway in ACC



DISCUSSION

In recent studies, the relationship between ER-stress and autophagy has generally been emphasized in the treatment of ACC, and ER-stress targeted processes have been focused on during the treatment process. Accordingly, there are publications showing that induction of autophagy with various agents in an ER-stress-mediated manner causes chemoresistance in ACC. For example, it has been shown that SAT-LB064 Mitotane, an FDA approved drug used in ACC treatment, causes ER stress, and triggers the autophagic pathway in H295R cells. It has been indicated that autophagy promotes cell survival in this situation, and it has been suggested that treatment success with mitotane may be reduced (Kenneth T., et al 2019). In another study, Tauroursodeoxycholic acid (TUDCA), known as the ER chemical chaperone, which has an ER-stress relieving effect, has been shown to trigger the ER-stress-mediated autophagy signaling pathway in ACC cells (Xuemei H. et al. 2019). As mentioned in a review article summarizing the role of autophagy in cancer formation and its importance in the treatment process in endocrine tumors, it has been stated that,autophagy is induced by the PPAR-γ agonist rosiglitazone (RGZ) and eventually the autophagic cell death is triggered in H295R cells belonging to ACC (Andrea W., et al 2015, Cerquetti L. et al 2011). In addition, it has been shown that the anticancer effect of cisplatin, which is an effective treatment

agent, is further increased when used with chloroquine in cells isolated from the tissues of patients diagnosed with ACC by inducing the autophagic process (Liang Q. et al 2016).

Although laboratory studies on ACC and possible treatment approaches have been conducted on a molecular and clinical level, the number of bioinformatics studies on survival analysis and possible genetic-based treatment approaches is quite limited. Because it is a rare type of cancer, there is not enough demographic data and gene level data for ACC patients in public sources. In our study, autophagy related genes have been identified by using gene density and demographic data of 43 ACC patients. It was concluded that most of the 222 ARGs (73 ARGs; 42 hazardous, 31 survival-triggering) significantly affect the survival of ACC patients. According to our results, suppression of genes with a HR greater than 1 (hazardous ARGs) with anticancer agents, and survival-triggering genes with a HR less than 1 can be tried in laboratory-based studies. In addition, the high number of ARGs that affect survival of ACC patients (32.89% of the genes out of 222 ARGs) highlights the importance of autophagy and associated biological processes in this rare and highly lethal type of cancer.

In our study, the biological significance of ARGs which are shown to affect the survival of ACC patients is investigated by GOrilla analysis. According to our results, the relationship with macrophagy and especially mitophagy-related biological processes is striking. Although there are current studies showing the importance of autophagy in ACC, which is one of the rare cancers, the number of studies specifically targeting mitochondrial processes is limited. For example, the agent known as ATR-101 (PD132301-02) has been observed to disrupt mitochondrial functions both *in vivo* and in ACC H295R cells (Yunhui C. et al 2016). In a recent study by Antonina Germano et al., it has been shown that mitotane used in the standard treatment of ACC has cytotoxic effects in *in vivo* and *in vitro* conditions, impairs mitochondrial functions and thus triggers apoptosis (Antonina G. et al 2020). In another study, it has been observed that mitochondrial membrane dysfunction occurred in cells with mitotane, and the apoptotic pathway was triggered (Ségolène. H. et al. 2017). In a recent review summarizing the mechanisms of action of mitotane treatment in ACC, it has been mentioned that mitotane has a cytotoxic effect on tumor tissue and provides the treatment by causing cell death and especially apoptotic cell death. Although it has been mentioned that it causes mitochondrial dysfunction among the mechanisms, mitophagy and macroautophagy processes have not been pointed out (Claudia RC. Et al 2020).

To our knowledge, among the research articles testing the treatment approaches in ACC, no studies specific to mitophagy have been found. Our results are important in identifying ARGs associated with prognosis associated with both macroautophagy and mitophagy, and by designing treatments targeting the identified genes, a personalized and effective cancer treatment can be provided in a rare ACC cancer. Thus, patients diagnosed with ACC, which is quite lethal and have a low survival rate, will have a chance to be treated more effectively. It is of great importance that the results of our study with the limited number of patients are validated at the gene level under laboratory conditions and transferred to clinical studies. Treatment types can be increased by directly targeting ARGs obtained from bioinformatics and survival analyses in our pre-laboratory work. As a conclusion, identification of prognosis related ARGs associated with both macroautophagy and mitophagy can lead to personalized and efficient cancer treatment in a rare cancer of ACC.

REFERENCES

1. Amaravadi RK, Lippincott-Schwartz J, Yin XM, et al. Principles and current strategies for targeting autophagy for cancer treatment. *Clin Cancer Res.* 2011;17(4). Doi:10.1158/1078-0432.CCR-10-2634
2. Andrea W., Fabio R., Antonio D., et al. Autophagy in endocrine tumors *Endocrine-Related Cancer* 2015;22(4) Doi: https://doi.org/10.1530/ERC-15-0042
3. Antonina G., Daniela R., Valerio L. Involvement of 27-Hydroxycholesterol in Mitotane Action on Adrenocortical Carcinoma *Cells* 2020;9(4). Doi:10.3390/cells9040885

4. Cerquetti L, Sampaoli C, Amendola D, et al. Rosiglitazone induces autophagy in H295R and cell cycle deregulation in SW13 adrenocortical cancer cells. *Experimental Cell Research* 2011;317(10). Doi:10.1016/j.yexcr.2011.02.014
5. Claudia RC., Alexandra A., Camila B. Pharmacological profile and effects of mitotane in adrenocortical carcinoma *British Journal of Clinical Pharmacology* 2020;12(31). Doi: 10.22541/au.159069174.47481624
6. Degenhardt K, Mathew R, Beaudoin B, et al. Autophagy promotes tumor cell survival and restricts necrosis, inflammation, and tumorigenesis. *Cancer Cell.* 2006;10(1). Doi:10.1016/j.ccr.2006.06.001
7. Kebebew E., Reiff E., Duh QY. et al. Extent of disease at presentation and outcome for adrenocortical carcinoma: have we made progress? *A World J Surg.* 2006;30(5).
8. Kenneth T.**,** Christina.**,** Adwitiya K. et al. SAT-LB064 Mitotane Induces Autophagy: A Mechanism to Promote Chemoresistance in Adrenocortical Carcinoma *Journal of the Endocrine Society*, 2019;3(1) https://doi.org/10.1210/js.2019-SAT-LB064
9. Levy JMM, Towers CG, Thorburn A. Targeting autophagy in cancer. *Nat Rev Cancer.* 2017;17(9). Doi:10.1038/nrc.2017.53
10. Levine B, Klionsky DJ. Development by self-digestion: Molecular mechanisms and biological functions of autophagy. *Dev Cell.* 2004;6(4). Doi:10.1016/S1534-5807(04)00099-1
11. Liang Q., Tianyuan X., Leilei X. Chloroquine enhances the efficacy of cisplatin by suppressing autophagy in human adrenocortical carcinoma treatment. *Drug Design, Development and Therapy* 2016:10. Doi: 10.2147/DDDT.S101701. eCollection 2016.
12. Marisa L., de Reyniès A., Duval A. et al. Gene expression classification of colon cancer into molecular subtypes: characterization, validation, and prognostic value. *PLoS Med* 2013;10(5): e1001453. PMID: 23700391
13. Rosella Libe Adrenocortical carcinoma (ACC): diagnosis, prognosis, and treatment *Front Cell Dev Biol.* 2015; 3: 45. doi: 10.3389/fcell.2015.00045
14. Ségolène H., Larbi A., Marie L. et al. Identifying mitotane-induced mitochondria-associated membranes dysfunctions: metabolomic and lipidomic approaches *Oncotarget*. 2017;8(66). Doi:10.18632/oncotarget.18968
15. White E, Karp C, Strohecker AM, et al. Role of autophagy in suppression of inflammation and cancer. *Curr Opin Cell Biol.* 2010;10(9). Doi:10.1016/j.ceb.2009.12.008
16. Wooten MD., King DK. Adrenal cortical carcinoma. Epidemiology and treatment with mitotane and a review of the literature. *Cancer*. 1993;72(11). Doi: 10.1002/1097-0142(19931201)72:11<3145::aid-cncr2820721105>3.0.co;2-n.
17. Xiao H., Xu D., Chen P., et al. Identification of Five Genes as a Potential Biomarker for Predicting Progress and Prognosis in Adrenocortical Carcinoma. *J Cancer.* 2018;9(23). Doi: 10.7150/jca.26698
18. Xuemei H., Lili W., Yaqi K. et al. auroursodeoxycholic acid mediates endoplasmic reticulum stress and autophagy in adrenocortical carcinoma cells *Oncol Lett.* 2019;18(6). Doi: 10.3892/ol.2019.11057
19. Yang ZJ, Chee CE, Huang S, et al. The role of autophagy in cancer: Therapeutic implications. *Mol Cancer Ther.* 2011:10(9). Doi:10.1158/1535-7163.MCT-11-0047
20. Yunhui C,, Raili Emilia K. ATR-101 disrupts mitochondrial functions in adrenocortical carcinoma cells and *in vivo Endocr Relat Cancer*. 2016;23(4). Doi: 10.1530/ERC-15-0527. Epub 2016 Feb 3.