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Investigation of Androgen Responsive Elements in Some Autophagy Related Genes via *In Silico* Analysis

Otofaji ile İlişkili Bazı Genlerdeki Androjen Cevap Elementlerinin *İn Silico* Analiz ile Araştırılması

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Abstract

Objective: Autophagy is a major cellular pathway that is responsible for removal of damaged organelles, misfolded or long-lived proteins by lysosome in eukaryotic cells, and it is a well conserved physiological mechanism from the yeast to mammalian. Autophagy is regulate many cellular process including cell death, cell development, tumor suppression, and also adaptation to nutrient deprivation. Autophagy has been associated with several pathologies, including neurodegenerative diseases, infectious diseases, metabolic diseases and cancer. Mammalian autophagy is regulated by 6 different protein complexes. These complexes are the ULK1–ATG13–FIP200–ATG101, VPS34-VPS15-Beclin1, WIPI/ATG18–ATG2 complex, the multi-spanning transmembrane protein ATG9A, the ubiquitin-like ATG5/ATG12 system, and the ubiquitin-like ATG8/LC3 conjugation system. These six-protein complex regulate different steps during autophagosome maturation, including vesicle nucleation, autophagosomal membrane elongation and integration of autophagosome. Recent studies highlight the role of autophagy in prostate cancer. Thus, it is important to understand the unknown processes about regulation of autophagy with its different mechanisms, especially androgen mediated regulation. In this study, our aim was to investigate the putative AREs in promoter sequence of autophagy related genes by in silico analysis.

Material-Method: Promoter sequences of the autophagy related target genes extracted from UCSC and EPD databases in FASTA format and then analyzed putative binding sites for androgen receptor binding motif (TGTTCTxxxAGAACA, AGAACAxxxAGAACA) by using V$GREF matrix from matinspector bioinformatics tool.

Results: The result of the in silico analysis indicates that putative AREs in the promoter region of 33 different genes associated with autophagy are identified.

Conclusions: Our data the positive correlation between suggest that autophagy related components may be tightly regulated by androgen signaling.

Keywords: Autophagy, Androgen Responsive Elements (Ares), Matinspector, Prostate Cancer, In Silico Analysis.

Özet

Amaç: Otofaji, hasarlı organellerin, hatalı katlanmış veya uzun ömürlü proteinlerin, ökaryotik hücrelerde lizozom aracılı uzaklaştırılmasından sorumlu olan majör bir hücresel yoldur ve mayadan memelilere kadar iyi düzeyde korunmuş fizyolojik mekanizmadır. Otofaji, hücre ölümü, hücre gelişimi, tümörün bastırılması ve ayrıca besin yoksunluğuna adaptasyon dahil birçok hücresel süreci düzenlemektedir. Otofaji, nörodejeneratif hastalıklar, bulaşıcı hastalıklar, metabolik hastalıklar ve kanserinde dahil olduğu çok çeşitli patolojilerle ilişkilendirilmiştir. Memeli otofajisi, 6 farklı protein kompleksi ile düzenlenmektedir. Bu kompleksler; ULK1 - ATG13 - FIP200 - ATG101, VPS34-VPS15-Beclin1, WIPI/ATG18 - ATG2 kompleksi, multi-spanning transmembran proteini ATG9A, ubikuitin benzeri ATG5/ATG12 sistemi ve ubitin-benzeri ATG8/ LC3 sistemidir. Bu altı protein kompleksi, vezikül nükleazasyonu, otofagozomal membran uzaması ve integrasyonunda dahil olduğu otofagazom olgunlaşmasını düzenlemektedir. Son çalışmalar otofajinin prostat kanserindeki rolünü vurgulamaktadır. Bu nedenle, otofajinin bilinmeyen mekanizmalar ile gerçekleşen regülasyonu ve özellikle androjen aracılı gerçekleşen regülasyonu hakkındaki bilinmeyen süreçlerin anlaşılması önem taşımaktadır. Bu çalışmada otofaji ile ilişkili genlerin promotor bölgesinde in silico analizler ile varsayılan ARE'leri araştırmayı amaçladık.

Materyal-Metot: Otofaji ile ilişkili hedef genlerin promotör dizileri UCSC ve EPD veri tabanından FASTA formatında ekstrakte edilerek, androjen resepötörü bağlanma motifi için varsayılan bağlanma bölgeleri V$GREF matrix'i kullanılarak matinspector biyoinformatik aracı ile analiz edildi.

Bulgular: İn silico analiz sonuçlara göre otofaji ile ilişkili 33 farklı genin promotor bölgesinde varsayılan ARE'ler tanımlandı.

Sonuç: Sonuçlarımız otofaji ile ilişkili komponentlerin androjen sinyalizasyonu ile sıkı şekilde düzenlenebileceğini önermektedir.

Anahtar kelimeler: Otofaji, Androjen Cevap Elementleri, Matinspector, Prostat Kanseri, İn Silico Analiz.

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Introduction

Autophagy is one of the most important and highly conserved physiological cellular process for degradation of misfolded proteins and damaged organelles. Besides protective and catabolic roles, autophagy has been shown to be associated with secretion (1,2). Basically, autophagy is a key player for cell death, cell development, tumor suppression, and also adaptation to nutrient deprivation (3). In recent years, different selective forms of autophagy have been characterized, including mitophagy, pexophagy, ER-phagy, lipophagy, aggrephagy, ribophagy and much more (4,5,6). However, autophagy has been associated with several pathologies, including neurodegenerative diseases, infectious diseases, metabolic diseases and cancer (7). The mechanism of autophagy initiates the formation of double membrane vesicles called autophagosome. These autophagosomes encapsulate the cytoplasmic components and its fused with lysosome to degradation of these components (8). That is, functional autophagy has a multi-step mechanism in which many proteins play a synchronized role. The so-called autophagy-related (ATG) genes and proteins are central to this process (9).

Mammalian autophagy is regulated by 6 different protein complexes. These complexes are the ULK1–ATG13–FIP200–ATG101, VPS34-VPS15-Beclin1, WIPI/ATG18–ATG2 complex, the multi-spanning transmembrane protein ATG9A, the ubiquitin-like ATG5/ATG12 system, and the ubiquitin-like ATG8/LC3 conjugation system. These six-protein complex regulate different steps during autophagosome maturation, including vesicle nucleation, autophagosomal membrane elongation and integration of autophagosome (10-15).

Prostate cancer is the second leading cause of cancer mortality among males and the incidence is very high compared to other types of cancer. Over 47,000 men are diagnosed with prostate cancer every year in the United Kingdom. On the other hand, this number is at approximately 3.3 million in the United States (16,17). The androgen receptor (AR) and androgen mediated signaling plays a critical role in any step of the development of normal prostate gland and also molecular pathogenesis of prostate cancer (18). After the androgen binding, AR dissociates from the chaperone complex proteins, forms a homodimeric structure through conformational change and is translocated into the nucleus. Once translocated into the nucleus, dimerized AR then acts as a ligand-dependent active transcription factor and regulate the gene expression by selectively binding to the consensus Androgen Response Element (ARE) sequences in the promoter or enhancer regions of target genes. Therefore, AREs have a critical role in the direct regulation of AR mediated gene expression (19,20). AREs contain two hexameric with a three base-pair spacer with a palindromic (5'-AGAACAxxxTGTTCT-3') or dihexameric (5'-AGAACAxxxAGAACA-3') repeats (21). Therefore, it is important to determine the putative AREs so that the regulation of different molecular pathways by androgen signaling can be understood.

Prostate cancer cells are also known to be have a high secretor capacity. In particular, proinflammatory cytokines such as IL-6 have been highly expressed in invasive prostate cancer types (22). Intact autophagy is required for the elaboration of secreted proinvasive factors (23). Therefore, it is of great importance to characterize the androgen mediated hormonal regulation of autophagy in prostate cancer. The number of publications establishing a link between link androgen receptor and autophagy has been constantly increasing. Nevertheless, there is a limited number of publications concerning the directly regulation of autophagy by AR. In 2017, Blessing et al. identified autophagic core members as ATG4B, ATG4D, ULK1, ULK2 and transcription factor TFEB, a master regulator of lysosomal biogenesis and function as novel androgen responsive genes (24).

In this study, in order to identify putative AREs, the thirty-three promoter regions of autophagy related genes by using matinspector bioinformatics tool were investigated (25). We defined 7 putative AREs for the ATG2A, 13 for ATG2B, 14 for ATG3, 12 for ATG4A, 8 for ATG4B, 10 for ATG4C, 10 for ATG4D, 8 for ATG5, 9 for ATG7, 11 for ATG9A, 9 for ATG9B, 19 for ATG10, 10 for ATG12, 1 for ATG13, 6 for ATG14, 11 for ATG16L1, 7 for ATG16L2, 6 for ATG101, 13 for BECN1, 7 for GABARAP, 5 for GABARAPL1, 12 for GABARAPL2, 7 for MAP1LC3A, 7 for MAP1LC3B2, 10 for MAP1LC3C, 3 for MAP1LC3B, 5 for RB1CC1, 11 for SNX4, 8 for SNX30, 10 for ULK1, 4 for ULK2, 15 for WIPI1 and 8 ARE for WIPI2 gene. The results of in silico analysis suggest that autophagy pathway may be tightly regulated via androgen signaling, and this process would give a new perspective to the treatment of prostate cancer.

Material and Methods

In Silico Analysis

Promoter sequences (from -9999 to +1) of the autophagy related target genes were accessed and extracted from University of California, Santa Cruz (UCSC) Genome Browser and Eukaryotic Promoter Database (EPD) in FASTA format (26). In an effort to find putative binding sites for androgen receptor binding motif (TGTTCTxxxAGAACA, AGAACAxxxAGAACA), the V$GREF matrix was selected from the matinspector bioinformatics tool (Genomatix Software, Munich, Germany, http://www.genomatix.de) and the threshold value was determined as 1.0. Located under the V$GREF matrix ARE.01, ARE.02, ARE.03, ARE.04 submatrices were used for prediction of putative AREs. Finally, AR specific binding sites for each autophagy related genes were indicated on the schematic promoter maps.

Results

In Silico Analysis Supports The Regulation Of Autophagy Related Genes Via Androgen Signaling

First, the members of 6 different protein complexes regulating mammalian autophagy were identified (Table 1), and then in order to identify the AREs on ULK1, ULK2, ATG2A, ATG2B, ATG3, ATG4A, ATG4B, ATG4C, ATG4D, ATG5, BECN1, ATG7, GABARAP, GABARAPL1, GABARAPL2, MAP1LC3A, MAP1LC3B, MAP1LC3B2, MAP1LC3C, ATG9A, ATG9B, ATG10, ATG12, ATG13, ATG14,

Table 1. Mammalian autophagy related proteins. Common mammalian autophagy related component names and synonyms are given, along with yeast orthologous

Gene symbol (Human)	Approval name	Synonyms	Gene symbol (yeast)	References
ULK1	unc-51 like autophagy activating kinase 1	ATG1; ATG1A; UNC51; hATG1; Unc51.1	Atg1a	(27)
ULK2	unc-51 like autophagy activating kinase 2	KIAA0623, Unc51.2, ATG1B	Atg1b	(27)
ATG2A	autophagy related 2A	KIAA0404	Atg2	(28)
ATG2B	autophagy related 2B	FLJ10242, C14orf103	Atg2	(28)
ATG3	autophagy related 3	PC3-96, FLJ22125, MGC15201, DKFZp564M1178, APG3L	Atg3	(27)
ATG4A	autophagy related 4A cysteine peptidase	AUTL2, APG4A	Atg4	(29)
ATG4B	autophagy related 4B cysteine peptidase	Apg4B, KIAA0943, DKFZp586D1822, AUTL1, APG4B	Atg4	(29)
ATG4C	autophagy related 4C cysteine peptidase	FLJ14867, AUTL3, AUTL1, APG4C	Atg4	(29)
ATG4D	autophagy related 4D cysteine peptidase	APG4-D, AUTL4, APG4D	Atg4	(29)
ATG5	autophagy related 5	ASP, APG5, hAPG5, APG5L, Apoptosis-specific protein	Atg5	(27)
BECN1	beclin1	ATG6, VPS30	Vps30/Atg6	(27)
ATG7	autophagy related 7	GSA7, DKFZp434N0735, APG7L	Atg7	(30)
GABARAP	GABA type A receptor-associated protein	ATG8A, MM46	Atg8	(31)
GABARAPL1	GABA type A receptor associated protein like 1	gec1, ATG8B, ATG8L, APG8L	Atg8	(31)
GABARAPL2	GABA type A receptor associated protein like 2	ATG8C, GATE-16, GATE16, ATG8, GEF2	Atg8	(31)
MAP1LC3A	microtubule associated protein 1 light chain 3 alpha	ATG8E, LC3A, MAP1BLC3, MAP1ALC3, LC3	Atg8	(32)
MAP1LC3B	microtubule associated protein 1 light chain 3 beta	ATG8F	Atg8	(32)
MAP1LC3B2	microtubule associated protein 1 light chain 3 beta 2	ATG8G	Ayg8	(32)
MAP1LC3C	microtubule associated protein 1 light chain 3 gamma	ATG8J	Atg8	(32)
ATG9A	autophagy related 9A	FLJ22169, APG9L1	Atg9a	(27)
ATG9B	autophagy related 9B	FLJ14885, APG9L2, SONE, NOS3AS	Atg9b	(27)
ATG10	autophagy related 10	DKFZP586I0418, FLJ13954, APG10L	Atg10	(32)
ATG12	autophagy related 12	APG12, APG12L		(27)
ATG13	autophagy related 13	KIAA0652	Atg13	(27)
ATG14	autophagy related 14	ATG14L, KIAA0831	Atg14	(27)
ATG16L1	autophagy related 16 like 1	WDR30, ATG16A, FLJ10035, APG16L, ATG16L	Atg16	(27)
ATG16L2	autophagy related 16 like 2	FLJ00012, ATG16B, WDR80	Atg16	(27)
RB1CC1	RB1 inducible coiled-coil 1	PPP1R131, DRAGOU14, FIP200, Cc1, KIAA0203, ATG17	Atg17	(27)
WIPI1	WD repeat domain, phosphoinositide interacting 1	FLJ10055, WIPI49, ATG18A, ATG18	Atg18a	(27)
WIPI2	WD repeat domain, phosphoinositide interacting 2	ATG21, FLJ12979, FLJ14217, DKFZp686P02188, CGI-50, ATG18B, DKFZP434J154, FLJ42984	Atg18b	(27)
SNX30	sorting nexin family member 30	ATG24A	Atg20	(27)
SNX4	sorting nexin 4	ATG24B	Atg24	(27)
ATG101	autophagy related 101	FLJ11773, C12orf44	-	(34)

Table 2. Mammalian autophagy related proteins. Common mammalian autophagy related component names and functional role within Autophagy is shown, in addition to chromosomal localization address, NCBI and HGNC Gene ID

Gene symbol (Human)	Function	Chromosomal localization	NCBI Gene ID	HGNC ID	References
ULK1	Ser/Thr protein kinase, Initiation of autophagy, mTORC1 binding partner	12q24.33	8408	HGNC:12558	(27)
ULK2	Ser/Thr protein kinase, Initiation of autophagy, mTORC1 binding partner	17p11.2	9706	HGNC:13480	(27)
ATG2A	WIPI4 interacting protein	11q13.1	23130	HGNC:29028	(28)
ATG2B	autophagosome formation and regulation of lipid droplet morphology and dispersion	14q32.2	55102	HGNC:20187	(28)
ATG3	Ubiquitin-like-conjugating enzyme, E2-like enzyme	3q13.2	64422	HGNC:20962	(27)
ATG4A	Cysteine protease, Deconjugating enzyme	Xq22.3	115201	HGNC:16489	(29)
ATG4B	Cysteine protease, Deconjugating enzyme	2q37.3	23192	HGNC:20790	(29)
ATG4C	Cysteine protease, Deconjugating enzyme	1p31.3	84938	HGNC:16040	(29)
ATG4D	Cysteine protease, Deconjugating enzyme	19p13.2	84971	HGNC:20789	(29)
ATG5	E3-like enzyme, Conjugated by ATG12	6q21	9474	HGNC:589	(27)
BECN1	core subunit of the PI3K complex I and II	17q21.31	8678	HGNC:1034	(27)
ATG7	E1-like enzyme	3p25.3	10533	HGNC:16935	(30)
GABARAP	ubiquitin-like protein, conjugated to PE	17p13.1	11337	HGNC:4067	(31)
GABARAPL1	ubiquitin-like protein, conjugated to PE	12p13.2	23710	HGNC:4068	(31)
GABARAPL2	ubiquitin-like protein, conjugated to PE	16q23.1	11345	HGNC:13291	(31)
MAP1LC3A	Ubiquitin-like protein conjugated to phosphatidylethanolamine (PE)	20q11.22	84557	HGNC:6838	(32)
MAP1LC3B	Ubiquitin-like protein conjugated to phosphatidylethanolamine (PE)	16q24.2	81631	HGNC:13352	(32)
MAP1LC3B2	Ubiquitin-like protein conjugated to phosphatidylethanolamine (PE)	12q24.22	643246	HGNC:34390	(32)
MAP1LC3C	Ubiquitin-like protein conjugated to phosphatidylethanolamine (PE)	1q43	440738	HGNC:13353	(32)
ATG9A	Transmembrane protein, Autophagasome assembly	2q35	79065	HGNC:22408	(27)
ATG9B	Transmembrane protein, Autophagasome assembly	7q36.1	285973	HGNC:21899	(27)
ATG10	E2-like conjugating enzyme	5q14.1-q14.2	83734	HGNC:20315	(32)
ATG12	E3-like enzyme, Ubiquitin like protein	5q22.3	9140	HGNC:588	(27)
ATG13	Subunit of the autophagy initiation complex, Links Atg17 to Atg1	11p11.2	9776	HGNC:29091	(27)
ATG14	Autophagy-specific subunit of the PtdIns3K complex	14q22.3	22863	HGNC:19962	(27)
ATG16L1	conjugation of phosphatidylethanolamine (PE), Interact with ATG5 and ATG12	2q37.1	55054	HGNC:21498	(27)
ATG16L2	conjugation of phosphatidylethanolamine (PE), Interact with ATG5 and ATG12	11q13.4	89849	HGNC:25464	(27)
RB1CC1	Scaffold for ULK1/2 and ATG13	8q11.23	9821	HGNC:15574	(27)
WIPI1	formation of pre-autophagosomal structures, PdtIns3K binding protein	17q24.2	55062	HGNC:25471	(27)
WIPI2	formation of pre-autophagosomal structures, PdtIns3K binding protein	7p22.1	26100	HGNC:32225	(27)
SNX30	Organelle autophagy	9q32	401518	HGNC:23685	(27)
SNX4	Organelle autophagy	3q21.2	8723	HGNC:11175	(27)
ATG101	ATG13-binding protein	12q13.13	60673	HGNC:25679	(34)

ATG16L1, ATG16L2, RB1CC1, WIPI1, WIPI2, SNX30, SNX4 and ATG101 promoter sites, the sequences from -9999 to +1 were determined using the database in UCSC and EPD and extracted in FASTA format, and specific binding motifs for AR were analyzed using matinspector bioinformatics tool (26).

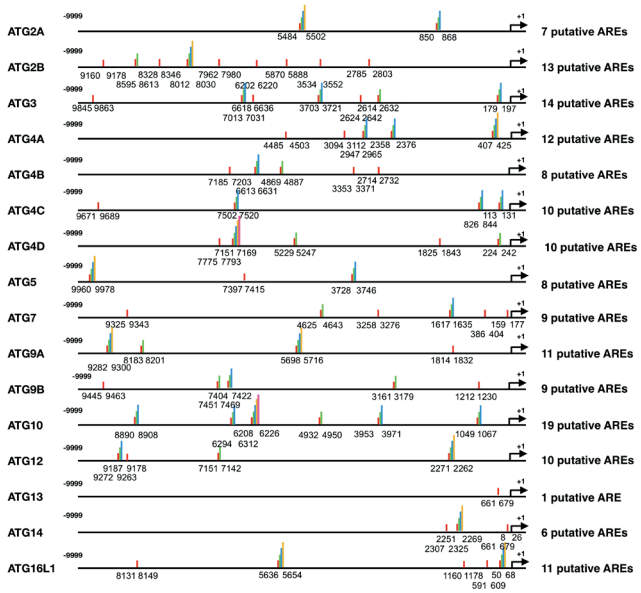

Figure 1. *In silico* analysis yielded different putative AREs in 33 promoter regions of autophagy related genes. Extracted promoter sequences were analyzed by matinspector bioinformatics tool. The ARE matrix (TGTTCTxxxAGAACA, AGAACAxxxAGAACA) was used to determine the regions where the androgen receptor would bind. Each colored bar refers to the different putative AREs in the same location

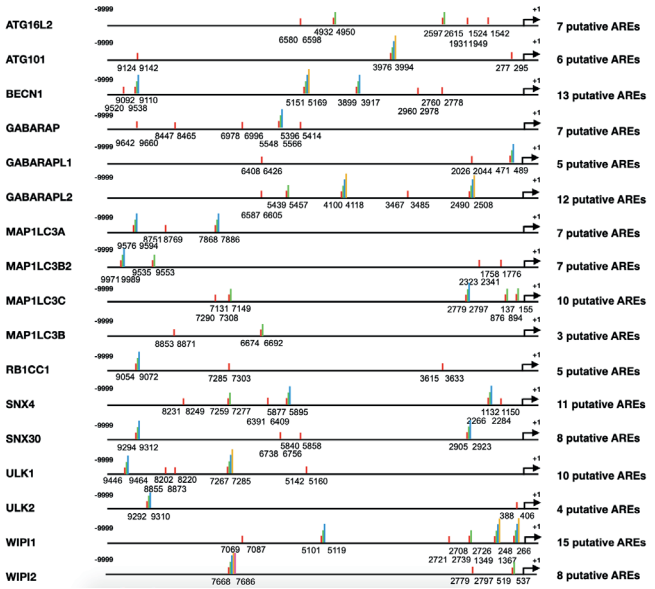

Figure 2. *In silico* analysis yielded different putative AREs in 33 promoter regions of autophagy related genes. Extracted promoter sequences were analyzed by matinspector bioinformatics tool. The ARE matrix (TGTTCTxxxAGAACA, AGAACAxxxAGAACA) was used to determine the regions where the androgen receptor would bind. Each colored bar refers to the different putative AREs in the same location.

ARE regions identified for thirty-three autophagy-related genes were presented in a list (Figure 1, 2). As it is indicated, numerous consensus AR binding sites were found. As a result of the analysis, 7 for ATG2A, 13 for ATG2B, 14 for ATG3, 12 for ATG4A, 8 for ATG4B, 10 for ATG4C, 10 for ATG4D, 8 for ATG5, 9 for ATG7, 11 for ATG9A, 9 for ATG9B, 19 for ATG10, 10 for ATG12, 1 for ATG13, 6 for ATG14, 11 for ATG16L1, 7 for ATG16L2, 6 for ATG101, 13 for BECN1, 7 for GABARAP, 5 for GABARAPL1, 12 for GABARAPL2, 7 for MAP1LC3A, 7 for MAP1LC3B2, 10 for MAP1LC3C, 3 for MAP1LC3B, 5 for RB1CC1, 11 for SNX4, 8 for SNX30, 10 for ULK1, 4 for ULK215 for WIPI1 and 8 putative AREs for WIPI2 were identified (Figure 1, 2) (Table 2) (Table 3), and the details of these regions were presented in an excel file (Supplementary Information).

Table 3. The number of putative AREs in promoter and near the promoter region of Autophagy related genes

Target Gene	Number of putative AREs
ATG2A	7 putative AREs
ATG2B	13 putative AREs
ATG3	14 putative AREs
ATG4A	12 putative AREs
ATG4B	8 putative AREs
ATG4C	10 putative AREs
ATG4D	10 putative AREs
ATG5	8 putative AREs
ATG7	9 putative AREs
ATG9A	11 putative AREs
ATG9B	9 putative AREs
ATG10	19 putative AREs
ATG12	10 putative AREs
ATG13	1 putative ARE
ATG14	6 putative AREs
ATG16L1	11 putative AREs
ATG16L2	7 putative AREs
ATG101	6 putative AREs
BECN1	13 putative AREs
GABARAP	7 putative AREs
GABARAPL1	5 putative AREs
GABARAPL2	12 putative AREs
MAP1LC3A	7 putative AREs
MAP1LC3B2	7 putative AREs
MAP1LC3C	10 putative AREs
MAP1LC3B	3 putative AREs
RB1CC1	5 putative AREs
SNX4	11 putative AREs
SNX30	8 putative AREs
ULK1	10 putative AREs
ULK2	4 putative AREs
WIPI1	15 putative AREs
WIPI2	8 putative AREs

Discussion

Autophagy is a major cellular pathway that is responsible for removal of damaged organelles, misfolded or long-lived proteins by lysosome in eukaryotic cells. In other words, autophagy is a self-digesting mechanism that plays a vital role for maintaining cellular homeostasis. Therefore, it is seen to be extremely well conserved in the evolutionary process (35). Autophagy is known to be the key player for cell death, cell development, tumor suppression, and also adaptation to nutrient deprivation. Besides protective and catabolic roles, autophagy has been shown to be associated with secretion (23). It is known that the disorders observed in autophagy have pathological effects, including neurodegenerative diseases, infectious diseases, metabolic diseases and cancer.

The autophagic pathway plays an important role in the secretion of proinvasive factors associated with invasion and migration (23). One of the major reasons for the failure of the treatment of cancer is the inability to prevent migration and invasive properties (36). Therefore, autophagy has become an important target for therapeutic approaches. There is limited information in the literature on androgen receptor mediated regulation of the autophagic pathway. Blessing et al. reported that the 4 core autophagy genes, which are ATG4B, ATG4D, ULK1 and ULK2, were transcriptional targets of the androgen receptor. In addition, TFEB, a master regulator of lysosomal biogenesis and function, has also been shown to be AR-mediated transcriptionally regulated (24), however, there is no any information about possible regulation of other autophagic members by directly AR. Apart from the direct transcriptional regulation of autophagy with AR, there are publications regarding the possible regulation via crosstalk with other cellular pathways. Androgens modulate autophagy via regulation of ER chaperone glucose-regulated protein 78/BiP in prostate cancer (37). On the other hand, a previous study indicated that AR promotes prostate cancer cell growth through autophagy down-regulation (38). In another study, increased ROS levels by androgen stimulation led to autophagic induction (39).

In accordance with the multistep process, 6 different protein complexes are involved in autophagy, respectively ULK1–ATG13–FIP200–ATG101, VPS34-VPS15-Beclin1, WIPI/ATG18–ATG2 complex, the multi-spanning transmembrane protein ATG9A, the ubiquitin-like ATG5/ATG12 system, and the ubiquitin-like ATG8/LC3 conjugation system (10-15). In this study, the possible regulation of selected autophagy related genes including ULK1, ULK2, ATG2A, ATG2B, ATG3, ATG4A, ATG4B, ATG4C, ATG4D, ATG5, BECN1, ATG7, GABARAP, GABARAPL1, GABARAPL2, MAP1LC3A, MAP1LC3B, MAP1LC3B2, MAP1LC3C, ATG9A, ATG9B, ATG10, ATG12, ATG13, ATG14, ATG16L1, ATG16L2, RB1CC1, WIPI1, WIPI2, SNX30, SNX4 and ATG101 via androgen signaling by matinspector bioinformatics tool was examined. The results demonstrate that the promoter regions (-9999 to +1) of autophagy-associated genes are putative ARE sequences.

Conclusion

Considering the fact that there is a lack of detailed information, and prominent / significant relationship between androgen signaling and autophagy has been a major limitation in the field of prostate cancer, there is a strong evidence that these in silico analysis results support that autophagy pathway may be regulated via androgen signaling, and this process would bring a new perspective to the treatment of prostate cancer. Although further studies are required to understand the role of androgens on autophagy in prostate cancer, these results support the critical roles of androgens on autophagy by via AR-associated transcriptionally regulation.

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