Distinct molecular profiles and potential therapeutic targets in androgen receptor stratified ovarian cancer patients

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Abstract

Objectives: Growing literature in breast cancer suggests that androgen receptor (AR) should be used to stratify patients with triple negative breast cancer (TNBC). Compared with AR+ TNBC, “quad negative” patients differ in their prognosis, response to therapy, and molecular profiles. It is unknown if AR status confers similar prognostic and treatment benefit in other tumor types. We aim to explore molecular and genomic features of AR+ and AR- ovarian cancer.

Methods: 8321 epithelial ovarian tumors were evaluated by Caris Life Sciences from 2009 to 2016 by multiplaform profiling, which included protein expression (IHC), NextGen sequencing (SEQ), and /or in-situ hybridization. AR expression higher than (1+, 10%) was determined positive. Antibody used for AR was AR27. Two-tailed Chi-square was used for comparison, significance was defined as $p < 0.05$.

Results: Overall, positive AR expression was seen in 39% of EOC tumors: 35% in serous, 32% in endometrioid, 21% in carcinosarcoma, 4.3% in mucinous and 3.9% in clear cell histologies. Compared to AR- tumors, AR+ tumors had significantly less frequent mutations on KRAS (4.6% vs. 10%, p=4.2E-11), PIK3CA (4.5% vs. 8%, p=1.85E-06), SMAD4 (0.1% vs. 0.5%, p=0.03) and GNAS (0 vs. 0.3%, p=0.03), and more frequent AKT1 (0.7% vs. 0.3%, p=0.03) mutations. Additionally, AR+ cohort showed significantly higher expression of ER (73% vs. 36%, p=3.1E-206), PR (41% vs. 17%, p=2.3E-116), lower frequency of PTEN loss by IHC (21% vs. 33%, p=4E-27), and lower frequency of TOP2A (IHC: 67% vs. 75%, p=6E-10; ISH: 0.9% vs. 6.7%, p=0.02), Her2 (1% vs. 2%, p=0.002; 2.1% vs. 3.9%, p=0.0003) and cMET (10% vs. 14.7%, p=1.8E-6; 0.w% vs. 0.9%, p=0.01) protein expression and gene amplification. In ER-/PR- cohort (N=3717), AR+ was seen in 9.9% of tumors. When AR+/ER-/PR- tumors were compared to AR-/ER-/PR- tumors, KRAS (1.5% vs. 10.8%, p=1.5E-6) and PIK3CA (3.4% vs. 9.3%, p=0.001) differences and cMET expression (11.3% vs. 19%, p=0.001) remain significant. Also, TP53 mutation rate was higher in the AR+ cohort compared to AR- (76% vs. 62%, p=7.7E-6).

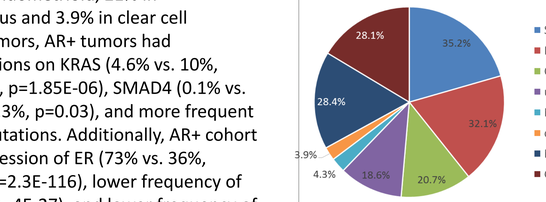
Conclusions: Our findings suggest distinct molecular profiles in AR stratified ovarian cancer, providing potential targets for therapeutic exploitation. Drugs targeting the PI3KCA/Akt/mTOR, MAPK, cMET, and cell cycle control pathways, as well as hormonal agents, may benefit selected subsets of patients stratified by AR expression.

Background

Growing literature in breast cancer suggests that androgen receptor (AR) should be used to stratify patients with triple negative breast cancer (TNBC). Compared with AR+ TNBC, “quad negative” patients differ in their prognosis, response to therapy, and molecular profiles. It is unknown if AR status confers similar prognostic and treatment benefit in other tumor types. We aim to explore molecular and genomic features of AR+ and AR- ovarian cancer.

Results

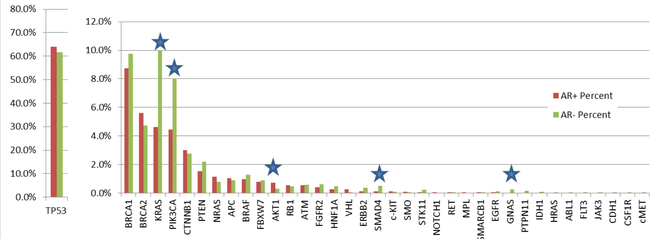
Figure 1. Overview of androgen receptor expression in 8321 epithelial ovarian tumors. Overall, positive AR expression was seen in 39% of EOC tumors (2338 of 8321): 35% in serous, 32% in endometrioid, 21% in carcinosarcoma, 4.3% in mucinous and 3.9% in clear cell histologies.



Histology	AR-Positive	Total	%
Serous	1693	4809	35.2%
Endometrioid	97	302	32.1%
Carcinosarcoma	59	285	20.7%
uncharacterized	396	2134	18.6%
Mucinous	9	208	4.3%
Clear cell	13	333	3.9%
Mixed Histology	71	250	28.4%
Grand Total	2338	8321	28.1%

Figure 2. Comparison of prevalence of gene mutations (2A) and protein expression/ gene amplifications (2B) in ovarian tumors that are AR positive and negative. A star indicates statistical significance using Chi-square test.

2A



2B

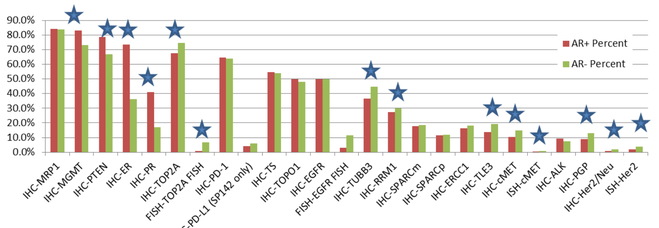
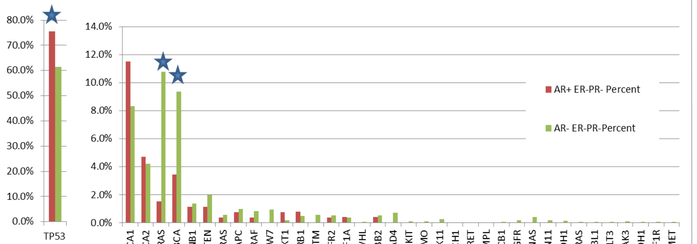


Figure 3. Comparison of prevalence of gene mutations (3A) and protein expression/ gene amplifications (3B) in ER-/PR- ovarian tumors that are AR positive and negative. A star indicates statistical significance using Chi-square test.

3A



3B

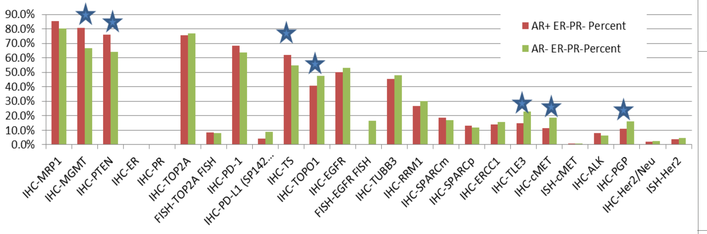


Table: Summary tables for mutation (upper) and IHC/ISH (lower) seen in AR+ and AR- groups for the complete cohort and the ER-/PR- cohort

	Complete cohort AR+/ AR-							ER-/PR- cohort: AR+/AR-						
	Mutated	Total	AR+ %	Mutated	Total	AR- %	p values	Mutated	Total	AR+ %	Mutated	Total	AR- %	p values
TP53	1061	1659	64.0%	2275	3688	61.7%		201	266	75.6%	1317	2140	61.5%	7.84E-06
BRCA1	96	1101	8.7%	205	2099	9.8%		22	191	11.5%	107	1286	8.3%	
BRCA2	62	1105	5.6%	99	2097	4.7%		9	192	4.7%	54	1284	4.2%	
KRAS	77	1666	4.6%	371	3710	10.0%	4.17E-11	4	266	1.5%	232	2153	10.8%	1.52E-06
PIK3CA	74	1661	4.5%	295	3672	8.0%	1.85E-06	9	263	3.4%	200	2142	9.3%	0.00131
CTNNB1	50	1670	3.0%	103	3714	2.8%		3	266	1.1%	29	2158	1.3%	
PTEN	25	1635	1.5%	80	3627	2.2%		3	263	1.1%	42	2112	2.0%	
NRAS	19	1667	1.1%	29	3698	0.8%		1	265	0.4%	12	2151	0.6%	
APC	17	1668	1.0%	33	3709	0.9%		2	264	0.8%	21	2158	1.0%	
BRAF	16	1668	1.0%	48	3714	1.3%		1	265	0.4%	18	2157	0.8%	
FBXW7	13	1656	0.8%	33	3684	0.9%		0	263	0.0%	20	2140	0.9%	
AKT1	12	1669	0.7%	11	3706	0.3%	0.028233	2	266	0.8%	4	2158	0.2%	
RB1	9	1642	0.5%	17	3663	0.5%		2	258	0.8%	10	2128	0.5%	
ATM	9	1663	0.5%	21	3687	0.6%		0	265	0.0%	12	2146	0.6%	
FGFR2	7	1667	0.4%	23	3701	0.6%		1	265	0.4%	11	2153	0.5%	
HNF1A	4	1517	0.3%	16	3262	0.5%		1	245	0.4%	7	1912	0.4%	
VHL	4	1532	0.3%	2	3426	0.1%		0	234	0.0%	1	1994	0.1%	
ERBB2	2	1648	0.1%	13	3655	0.4%		1	261	0.4%	11	2135	0.5%	
SMAD4	2	1666	0.1%	19	3700	0.5%	0.032685	0	266	0.0%	15	2149	0.7%	
c-KIT	2	1671	0.1%	3	3707	0.1%		0	266	0.0%	2	2155	0.1%	
SMO	1	1399	0.1%	2	3107	0.1%		0	220	0.0%	2	1817	0.1%	
STK11	1	1579	0.1%	8	3485	0.2%		0	243	0.0%	5	2028	0.2%	
NOTCH1	1	1635	0.1%	0	3609	0.0%		0	262	0.0%	0	2098	0.0%	
RET	1	1649	0.1%	2	3678	0.1%		0	261	0.0%	0	2143	0.0%	
MPL	1	1652	0.1%	0	3673	0.0%		0	265	0.0%	0	2132	0.0%	
SMARCB1	1	1654	0.1%	1	3696	0.0%		0	264	0.0%	1	2151	0.0%	
EGFR	1	1666	0.1%	4	3704	0.1%		0	265	0.0%	4	2153	0.2%	
GNAS	0	1670	0.0%	10	3716	0.3%	0.033847	0	266	0.0%	9	2158	0.4%	
PTPN11	0	1666	0.0%	6	3710	0.2%		0	266	0.0%	4	2156	0.2%	
IDH1	0	1671	0.0%	3	3717	0.1%		0	266	0.0%	3	2159	0.1%	
HRAS	0	1451	0.0%	2	3199	0.1%		0	236	0.0%	1	1873	0.1%	
ABL1	0	1608	0.0%	2	3598	0.1%		0	259	0.0%	1	2091	0.0%	
FLT3	0	1663	0.0%	2	3698	0.1%		0	265	0.0%	1	2149	0.0%	
JAK3	0	1662	0.0%	2	3699	0.1%		0	265	0.0%	2	2151	0.1%	
CDH1	0	1664	0.0%	2	3704	0.1%		0	266	0.0%	1	2154	0.0%	
CSF1R	0	1663	0.0%	1	3704	0.0%		0	266	0.0%	1	2152	0.0%	
cMET	0	1669	0.0%	1	3713	0.0%		0	266	0.0%	1	2158	0.0%	

	Positive	Total	AR+ %	Positive N	Total	AR- %	p values	Positive	Total	AR+ %	Positive	Total	AR- %	p values
IHC-MRP1	238	283	84.1%	855	1022	83.7%		35	41	85.4%	416	519	80.2%	
IHC-MGMT	1927	2321	83.0%	4331	5912	73.3%	9.86E-21	295	365	80.8%	2209	3316	66.6%	3.33E-08
IHC-PTEN	1819	2309	78.8%	3940	5911	66.7%	4E-27	278	365	76.2%	2114	3306	63.9%	3.32E-06
IHC-ER	1717	2338	73.4%	2163	5983	36.2%	3.1E-206	0	369	0.0%	0	3348	0.0%	
IHC-PR	956	2338	40.9%	1022	5983	17.1%	2.3E-116	0	369	0.0%	0	3348	0.0%	
IHC-TOP2A	1389	2060	67.4%	3913	5245	74.6%	6.11E-10	255	338	75.4%	2287	2968	77.1%	
FISH-TOP2A	1	114	0.9%	21	312	6.7%	0.015654	1	12	8.3%	15	185	8.1%	
IHC-PD-1	794	1229	64.6%	1598	2499	63.9%		155	227	68.3%	980	1535	63.8%	
IHC-PD-L1 (SP142)	20	488	4.1%	62	1012	6.1%		4	91	4.4%	53	605	8.8%	
IHC-TS	1190	2173	54.8%	2998	5544	54.1%		217	350	62.0%	1724	3142	54.9%	0.010875
IHC-TOPO1	1078	2167	49.7%	2637	5506	47.9%		142	347	40.9%	1484	3124	47.5%	0.019771
IHC-EGFR	473	951	49.7%	981	1961	50.0%		83	165	50.3%	632	1189	53.2%	
FISH-EGFR FISH	1	32	3.1%	9	78	11.5%		0	2	0.0%	6	36	16.7%	
IHC-TUBB3	687	1875	36.6%	2018	4510	44.7%	2.38E-09	141	310	45.5%	1254	2617	47.9%	
IHC-RRM1	507	1850	27.4%	1471	4928	29.8%	0.048605	79	294	26.9%	837	2766	30.3%	
IHC-SPARCm	285	1607	17.7%	816	4382	18.6%		44	237	18.6%	407	2388	17.0%	
IHC-SPARCp	198	1735	11.4%	551	4677	11.8%		35	263	13.3%	305	2576	11.8%	
IHC-ERCC1	271	1662	16.3%	704	3908	18.0%		39	279	14.0%	359	2271	15.8%	
IHC-TLE3	273	1987	13.7%	923	4792	19.3%	5.66E-08	46	313	14.7%	623	2737	22.8%	0.001088
IHC-cMET	210	2020	10.4%	718	4884	14.7%	1.83E-06	37	326	11.3%	520	2781	18.7%	0.001066
ISH-cMET	4	1555	0.3%	31	3558	0.9%	0.0143	2	259	0.8%	18	2065	0.9%	
IHC-ALK	47	497	9.5%	73	959	7.6%		7	88	8.0%	37	583	6.3%	
IHC-PGP	182	2038	8.9%	675	5136	13.1%	7.02E-07	37	331	11.2%	467	2916	16.0%	0.021282
IHC-Her2/Neu	23	2337	1.0%	117	5978	2.0%	0.001936	8	368	2.2%	83	3344	2.5%	
ISH-Her2	40	1895	2.1%	181	4629	3.9%	0.0003	11	295	3.7%	119	2623	4.5%	

Conclusions

- Our findings suggest distinct molecular profiles in AR stratified ovarian cancer, providing potential targets for therapeutic exploitation.
- Drugs targeting the PI3KCA/Akt/mTOR, MAPK, cMET, and cell cycle control pathways, as well as hormonal agents, may benefit selected subsets of patients stratified by AR expression.

References

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