Clinico-pathological and molecular features associated with TP53 mutation in 3457 molecularly-profiled colorectal cancers (CRCs)

Joanne Xiu[1], Thierry Soussi[2,3], Sandeep Reddy[1]and Wafik S. El-Deiry[4]

[1]Caris Life Sciences, Phoenix, AZ, USA; [2]Department of Oncology-Pathology, Karolinska Institutet, Stockholm, Sweden; [3]INSERM, Paris, France; [4]Laboratory of Translational Oncology and Experimental Cancer Therapeutics, Department of Hematology/Oncology and Molecular Therapeutics Program, Fox Chase Cancer Center, Philadelphia, PA, USA

Abstract #1591

Background: Deregulation of the p53 tumor suppressor gene (TP53) is a key event contributing to transformation and aggressive metastatic features of CRC. Patients with TP53 mutation are often resistant to therapy and carry a poor prognosis.

Method: We investigated TP53 mutation in a cohort of 3457 CRCs to identify molecular features specific to TP53-mutated CRC tumors. The 3457 CRC clinical samples were evaluated for tumor profiling (Caris Life Sciences, Phoenix, AZ). Tests included Sanger or next generation sequencing (NGS), protein expression by immunohistochemistry (IHC) and gene amplification by in situ hybridization (ISH).

Results: TP53 mutation was observed in 2106 or 61% of CRCs analyzed. 2018 or 96% of these mutant TP53 tumors carried one TP53 mutation, while 83 (4%) carried 2 mutations, 4 and 1 tumors carried 3 and 4 mutations per tumor, respectively. Among the 2200 mutations found in TP53, 37% were found at one of the six hotspots within the DNA binding domain (R175, G245, R248, R249, R273 and R282). Overall, 1554 (71%) were missense mutations, 367 (17%) nonsense, 209 (9.5%) frameshift, 45 (2%) small in-dels, and 25 (1.1%) mutations that affect splicing. In this cohort, TP53 mutation was more prevalent in male patients (64% vs. 57%, P<0.0001) and was more likely to occur in tumors that originated from the left colon (69%) as compared to the right colon (45%, p<0.0001). TP53 mutation rate was not correlated with patient age, histology or whether the tumor sample was taken from the primary or metastatic sites. When the molecular features of TP53-mutated tumors were compared to those of wild-type TP53, mutated tumors carried significantly higher Her2 IHC expression (2.5% vs. 1.0%, p=0.0039) and gene amplification (3.7% vs. 1.4%, p=0.0002), as well as higher MGMT (61% vs. 53%, p<0.0001) and TOPO2A expression (92% vs. 81%, p<0.0001). On the other hand, lower EGFR expression (57.4% vs. 70%, p<0.0001), PTEN expression (47.9% vs. 61%, p<0.0001), microsatellite instability (2.5% vs. 11.5%, p<0.0001), ERCC1 (18% vs. 24%, p<0.0001) and TS expression (31% vs. 38%, p<0.0001) were associated with TP53-mutated tumors. TP53-mutated CRCs carried higher rates of APC mutation (63% vs. 53%, p<0.0001), but lower rates of KRAS (46% vs. 54%, p<0.0001), PIK3CA (11.6% vs. 22%, p<0.0001), PTEN (2% vs. 5.2%, p<0.0001) , GNAS (1% vs. 8.3%, p<0.0001) and AKT1 (0.6% vs. 1.7%, p=0.0016) mutation.

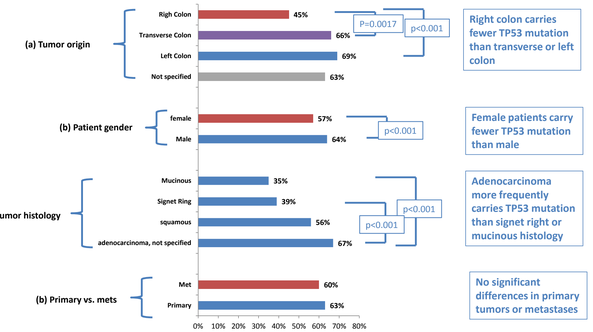
Conclusion: In a cohort of 3457 molecularly profiled CRCs, TP53 mutation was more prevalent in males and tumors that originated from the left colon. Distinct molecular features associated with TP53 mutation in CRC included lower frequency of PI3K/Akt/mTor pathway activation manifested by significantly lower frequency of PIK3CA, PTEN and AKT1 mutations and higher Her2 overexpression and amplification. Our findings suggest differential presence of therapeutic targets in CRC tumors based on TP53 mutation status.

Results:

1. Characteristics of 3457 tumors included in the analysis

		TP53 MT		TP53 WT		Total
Tumor Origin	Left Colon	705	69%	310	31%	1015
	Right Colon	338	45%	411	55%	749
	Transverse Colon	42	66%	22	34%	64
	Not specified	1021	63%	608	37%	1629
Gender	Male	1144	64%	637	36%	1781
	Female	962	57%	714	43%	1676
Age	Average Age	58.9		60.6		
Histology	Mucinous	197	35%	363	65%	560
	Signet Ring	59	39%	94	61%	153
	Squamous	5	56%	4	44%	9
	Adenocarcinoma, not specified	1874	67%	931	33%	2805
Met/Primary	Met	1045	60%	691	40%	1736
	Primary	1015	63%	609	38%	1624
	Not specified	46	47%	51	53%	97

2. Mutations of TP53 and tumor location (a), patient gender (b), tumor histology (c), and primary vs. metastasis (d)



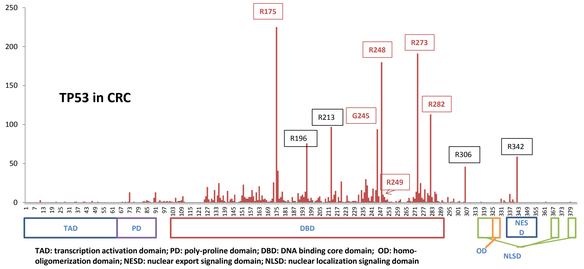
Right colon carries fewer TP53 mutation than transverse or left colon

Female patients carry fewer TP53 mutation than male

Adenocarcinoma more frequently carries TP53 mutation than signet right or mucinous histology

No significant differences in primary tumors or metastases

3. Structural distributions of TP53 mutations found in the CRC cohort. The X axis represents the position on the TP53 gene; the Y axis shows the counts of mutations found at a particular position. Hotspot mutations known to affect DNA contact (R248, R273) or cause structural disruption (R175, G245, R249 and R282) are marked in red; additional nonsense mutations seen at high frequencies marked in black.



TAD: transcription activation domain; PD: poly-proline domain; DBD: DNA binding core domain; OD: homo-oligomerization domain; NESD: nuclear export signaling domain; NLSD: nuclear localization signaling domain

4. Details on the most frequent TP53 mutations observed and the types of mutation

(a)Tumor Origin	R175	R196	R213	G245	R248	R273	R282	R306	R342
Right	24	7	14	20	41	27	23	8	13
Transverse	4	1	5	1	4	3	3		4
Left	70	39	27	40	54	63	41	21	18
NOS	127	30	51	34	81	98	46	16	24
Grand Total	225	76	97	94	180	191	113	45	59

Mutations at these locations are more likely to occur in the left colon compared to the right colon

(b) Patient Gender	R175	R196	R213	G245	R248	R273	R282	R306	R342
Female	97	33	43	45	83	96	50	27	35
Male	128	43	54	49	97	95	63	18	24
Grand Total	225	76	97	94	180	191	113	45	59

While overall TP53 mutations are more likely to occur in male, R273 (p=non significant), R306(p=ns) and R342 (p=0.035) mutations are more likely to occur in female patients.

(c)Histology	R175	R196	R213	G245	R248	R273	R282	R306	R342
Adenocarcinoma, NOS	196	67	82	80	158	169	104	42	50
Mucinous	25	4	11	10	17	12	7	2	4
Mucinous | signet		1	3		3	7			3
Signet-ring	3	4	1	4	2	3	2	1	1
Squamous	1								1
Grand Total	225	76	97	94	180	191	113	45	59

Adenocarcinoma carries the highest TP53 mutation frequencies

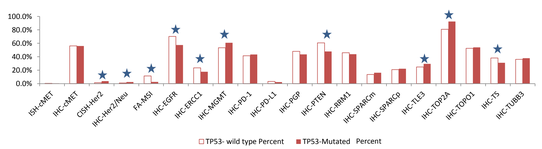
(d) Primary vs. Met	R175	R196	R213	G245	R248	R273	R282	R306	R342
Primary	90	36	47	53	86	87	63	19	33
Met	131	39	45	40	89	98	48	25	26
n/a	4	1	5	1	5	6	2	1	
Grand Total	225	76	97	94	180	191	113	45	59

R175 mutations are more likely to be found in metastatic sites than in the primary tumors (p=0.008)

(e)Mutation Type	R175	R196	R213	G245	R248	R273	R282	R306	R342
Frameshift		1		3	3	3			2
Missense	225	1	14	91	177	190	113		
Small indel									
Splice									
Truncating		74	83					45	57
Grand Total	225	76	97	94	180	191	113	45	59

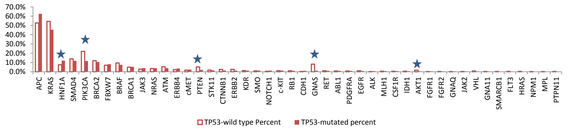
Majority of the mutations observed at the hotspots are missense mutations; nonsense mutations are observed frequently at R196, R213, R306 and R342

5. Molecular profile comparison of TP53 mutated and TP53-WT CRC tumors tested by IHC and ISH. A star indicates the differences are statistically significant (p<0.05) by Chi-square test.



	TP53-wild type			TP53-Mutated			
	Positive N	Total N	Percent	Positive N	Total N	Percent	p values
ISH-cMET	4	918	0.4%	7	1482	0.5%	
IHC-cMET	658	1172	56.1%	1009	1801	56.0%	
CISH-Her2	15	1100	1.4%	62	1674	3.7%	0.0002
IHC-Her2/Neu	12	1188	1.0%	45	1834	2.5%	0.0039
FA-MSI	68	592	11.5%	25	992	2.5%	<0.0001
IHC-EGFR	415	591	70.2%	596	1038	57.4%	<0.0001
IHC-ERCC1	85	362	23.5%	106	601	17.6%	<0.0001
IHC-MGMT	628	1177	53.4%	1099	1810	60.7%	<0.0001
IHC-PD-1	322	776	41.5%	550	1269	43.3%	
IHC-PD-L1	26	778	3.3%	30	1274	2.4%	
IHC-PGP	556	1160	47.9%	774	1778	43.5%	
IHC-PTEN	719	1185	60.7%	875	1826	47.9%	<0.0001
IHC-RRM1	444	965	46.0%	621	1420	43.7%	
IHC-SPARCm	109	797	13.7%	180	1111	16.2%	
IHC-SPARCp	182	873	20.8%	279	1262	22.1%	
IHC-TLE3	292	1176	24.8%	532	1804	29.5%	0.0057
IHC-TOP2A	919	1137	80.8%	1648	1785	92.3%	<0.0001
IHC-TOPO1	614	1171	52.4%	976	1808	54.0%	
IHC-TS	455	1193	38.1%	575	1855	31.0%	<0.0001
IHC-TUBB3	425	1178	36.1%	686	1814	37.8%	

6. Molecular profile comparison of TP53-mutated and TP53-WT CRC tumors tested by NextGen Sequencing. A star indicates the differences are statistically significant (p<0.05) by Chi-square test.



	TP53- wild type			TP53-Mutated			
	Mutated N	Total N	Percent	Mutated N	Total N	Percent	p values
APC	706	1339	52.7%	1305	2085	62.6%	
KRAS	727	1337	54.4%	949	2088	45.5%	
HNF1A	93	1218	7.6%	228	1887	12.1%	<0.0001
SMAD4	188	1347	14.0%	244	2063	11.8%	
PIK3CA	292	1323	22.1%	238	2055	11.6%	<0.0001
BRCA2	66	549	12.0%	104	990	10.5%	
FBXW7	95	1334	7.1%	169	2059	8.2%	
BRAF	128	1349	9.5%	156	2092	7.5%	
BRCA1	27	546	4.9%	53	988	5.4%	
JAK3	39	1341	2.9%	84	2082	4.0%	
NRAS	47	1343	3.5%	82	2072	4.0%	
ATM	72	1332	5.4%	79	2045	3.9%	
ERBB4	32	1339	2.4%	75	2071	3.6%	
cMET	25	1351	1.9%	48	2090	2.3%	
PTEN	67	1299	5.2%	41	2001	2.0%	<0.0001
STK11	23	1303	1.8%	30	2022	1.5%	
CTNNB1	35	1351	2.6%	29	2093	1.4%	
ERBB2	35	1331	2.6%	27	2057	1.3%	
KDR	17	1344	1.3%	27	2067	1.3%	
SMO	11	1180	0.9%	24	1840	1.3%	
NOTCH1	8	1330	0.6%	26	2040	1.3%	
c-KIT	16	1347	1.2%	26	2076	1.3%	
RB1	15	1339	1.1%	22	2069	1.1%	

	TP53- wild type			TP53-Mutated			
	Mutated N	Total N	Percent	Mutated N	Total N	Percent	p values
CDH1	5	1344	0.4%	22	2087	1.1%	
GNAS	111	1340	8.3%	22	2096	1.0%	<0.0001
RET	14	1325	1.1%	21	2038	1.0%	
ABL1	11	1303	0.8%	20	2021	1.0%	
PDGFRA	12	1326	0.9%	19	2048	0.9%	
EGFR	15	1346	1.1%	17	2080	0.8%	
ALK	2	1351	0.1%	17	2092	0.8%	
MLH1	9	1348	0.7%	17	2094	0.8%	
CSF1R	7	1346	0.5%	15	2063	0.7%	
IDH1	9	1350	0.7%	13	2094	0.6%	
AKT1	23	1342	1.7%	12	2085	0.6%	0.0016
FGFR1	3	1350	0.2%	11	2094	0.5%	
FGFR2	5	1345	0.4%	10	2073	0.5%	
GNAQ	1	1027	0.1%	8	1704	0.5%	
JAK2	5	1349	0.4%	9	2086	0.4%	
VHL	11	1251	0.9%	8	1927	0.4%	
GNA11	4	1166	0.3%	6	1845	0.3%	
SMARCB1	5	1343	0.4%	6	2071	0.3%	
FLT3	6	1350	0.4%	5	2082	0.2%	
HRAS	5	1192	0.4%	4	1845	0.2%	
NPM1	1	1340	0.1%	3	2078	0.1%	
MPL	1	1344	0.1%	3	2080	0.1%	
PTPN11	5	1347	0.4%	3	2090	0.1%	

Conclusions

- Analysis in a large of colorectal cancer cohort reveals that TP53 mutations are seen in 61% of tumors and is associated with clinico-pathological features including tumor origin (left and transverse colon), patient gender (higher in male) and tumor histology (highest in adenocarcinoma).
- Hotspot mutations previously known to affect DNA contact or cause structural disruption are seen at highest frequencies in our cohort, mutations in the DNA binding domain as well as nuclear export domain are also seen at high frequencies, which warrants further investigation. Future research will also include comparison with published TP53 database.
- While overall TP53 mutations are more likely to occur in male, mutations including R342 mutations are more likely to occur in female patients (p=0.035). While overall TP53 mutations occur at similar frequency in primary tumors and metastases, R175 mutations are more likely to be found in metastatic sites than in the primary tumors (p=0.008)
- Distinct molecular features associated with TP53 mutation in CRC included lower frequencies of microsatellite instability, lower frequency of PI3K/Akt/mTOR pathway activation manifested by significantly lower frequency of PIK3CA, PTEN and AKT1 mutations and higher Her2 overexpression and amplification.
- Our findings suggest differential presence of therapeutic targets in CRC tumors based on TP53 mutation status.

References

- *Li XL, Zhou J, Chen ZR, Chng WJ. P53 mutations in colorectal cancer - molecular pathogenesis and pharmacological reactivation. World J Gastroenterol. 2015 Jan 7;21(1):84-93.*
- *Brown CJ, Lain S, Verma CS, Fersht AR, Lane DP. Awakening guardian angels: drugging the p53 pathway. Nat Rev Cancer. 2009 Dec;9(12):862-73.*

AACR Annual Meeting
American Association for Cancer Research
2016 • NEW ORLEANS
April 16-20