The landscape of DNA damage response (DDR) pathway in colorectal cancer (CRC)

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Abstract ID: 4064

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Introduction

Abnormal DDR is a hallmark of cancer, relating to genome instability, anti-tumor immunity, and sensitivity to chemotherapeutic agents and radiation [1-5]. We conducted a large-scale investigation to clarify the alteration of DDR pathway in CRC.

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2. William M Grady. et al. Gastroenterology. 2008. 135:1079-99.
3. Sato H, et al. Nature Communications. 2017. 8:1751.
4. Sen T, et al. Cancer Discovery. 2019. 9:646-61.
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Method

- Tumor samples from 9321 CRC patients were retrospectively reviewed.
- Next-Generation Sequencing (NGS) on a custom-designed panel enriching 592 gene targets was performed.
- Samples with mutations detected in any of 29 DDR-related genes were deemed DDR-mutant (DDR-MT); the rest DDR-wild type (DDR-WT).
- Microsatellite instability (MSI) status was tested with a combination of immunohistochemistry (IHC), fragment analysis and NGS.
- Tumor mutational burden (TMB) was calculated based on somatic nonsynonymous missense mutations.
- PD-L1 was tested by IHC (SP142).
- Consensus molecular subtype (CMS) was developed using RNA sequencing data.

29 DDR-related genes

DDR pathways		
	HR	*BAP1*
		BARD1
		BLM
		BRCA1
		BRCA2
		BRIP1
		CDK12
		MRE11
		NBN
		PALB2
		RAD50
		RAD51
		RAD51B
		WRN
	NHEJ	*PRKDC*
	CP	*ATM*
		ATR
		CHEK1
		CHEK2
	FA	*FANCA*
		FANCC
		FANCD2
		FANCE
		FANCF
		FANCG
		FANCL
	SSB repair	*ERCC1*
		XPA
		XPC

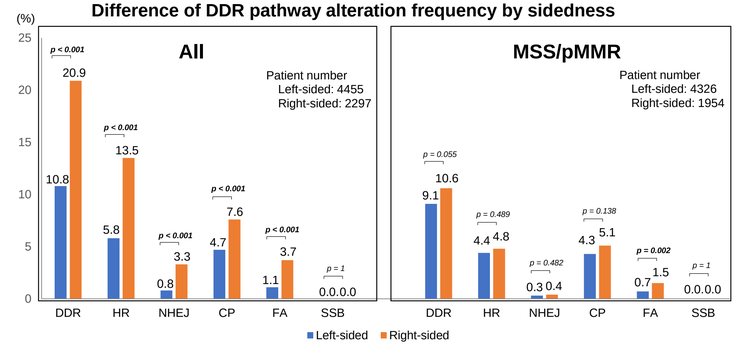
<Abbreviations>
HR: homologous recombination
NHEJ: non-homologous end joining
CP: checkpoint
FA: Fanconi anemia
SSB: single strand break

Results

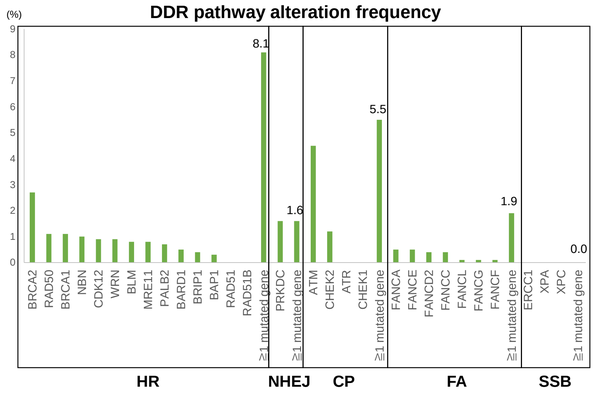
Patient characteristics

	Total	DDR-MT	DDR-WT	*P*-velue (DDR-MT vs WT)
Patient number	9321	1290 (13.8%)	8031	
Median age (range)	60 (14-90+)	62 (16-90+)	60 (14-90+)	**0.008**
Sex				
Male	5011 (53.8%)	637 (49.4%)	4374 (54.5%)	**<0.001**
Female	4310 (46.2%)	653 (50.6%)	3657 (45.5%)	
Primary tumor location				
Left	4455 (47.8%)	482 (37.4%)	3973 (49.5%)	**<0.001**
Right	2297 (24.6%)	479 (37.1%)	1818 (22.6%)	
Unclear	2569 (27.6%)	329 (25.5%)	2240 (27.9%)	
MSI/MMR status				
MSI-H/dMMR	597 (6.4%)	456 (35.3%)	141 (1.8%)	**<0.001**
MSS/pMMR	8702 (93.4%)	829 (64.3%)	7873 (98.0%)	
Unclear	22 (0.2%)	5 (0.4%)	17 (0.2%)	

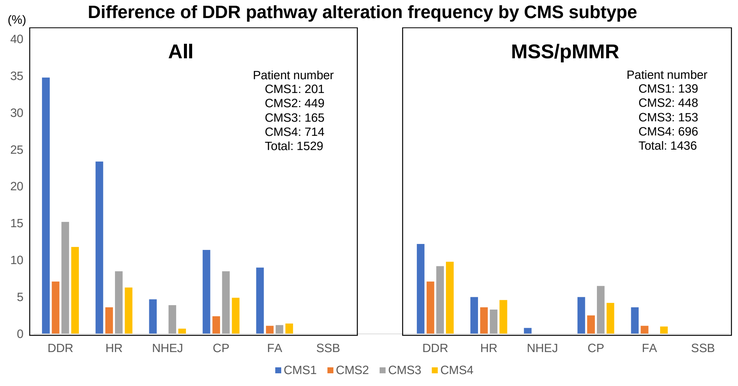
Difference of DDR pathway alteration frequency by sidedness



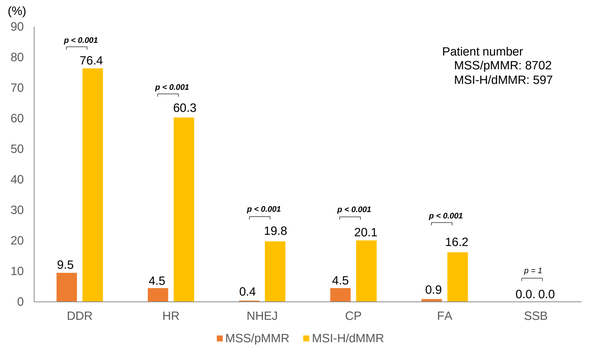
DDR pathway alteration frequency



Difference of DDR pathway alteration frequency by CMS subtype



Difference of DDR pathway alteration frequency by MSI/MMR status



Comparison of DDR-MT and DDR-WT on major gene mutations and immune profiles

	All			MSS/pMMR			MSI-H/dMMR		
	DDR-MT (N = 1290)	DDR-WT (N = 8031)	*P*-value	DDR-MT (N = 829)	DDR-WT (N = 7873)	*P*-value	DDR-MT (N = 456)	DDR-WT (N = 141)	*P*-value
TP53	48.2%	76.1%	**<0.001**	55.8%	76.9%	**<0.001**	34.8%	32.9%	0.679
APC	60.5%	74.5%	**<0.001**	70.4%	75.1%	**0.004**	42.3%	46.1%	0.429
KRAS	44.0%	49.8%	**<0.001**	52.6%	50.2%	0.187	27.9%	27.0%	0.834
ARID1A	55.0%	19.1%	**<0.001**	22.4%	16.7%	**0.042**	74.4%	72.9%	0.774
PIK3CA	22.6%	15.8%	**<0.001**	18.0%	15.6%	0.077	30.9%	26.2%	0.288
SMAD4	12.1%	12.3%	0.771	15.3%	12.4%	**0.017**	6.4%	9.9%	0.152
FBXW7	17.5%	8.5%	**<0.001**	11.5%	8.2%	**0.002**	28.2%	24.6%	0.417
BRAF	20.4%	7.3%	**<0.001**	8.0%	6.8%	0.188	43.3%	34.3%	0.058
RNF43	25.7%	3.0%	**<0.001**	3.4%	2.3%	**0.043**	66.4%	41.8%	**<0.001**
AMER1	9.5%	5.1%	**<0.001**	6.7%	5.3%	0.107	14.8%	12.1%	0.438
TMB (mean)	20.9/Mb	7.7/Mb	**<0.001**	13.7/Mb	7.6/Mb	**0.017**	54.5/Mb	27.8/Mb	**<0.001**
TMB-H (≥17)	38.1%	2.1%	**<0.001**	5.6%	0.6%	**<0.001**	97.1%	84.1%	**<0.001**
PD-L1 ≥5%	10.1%	2.7%	**<0.001**	4.8%	2.4%	**<0.001**	19.8%	20.4%	0.874

Summary

- **Of 9321 cases, 1290 (13.8%) were DDR-MT.**
- **Alteration frequency in HR, NHEJ, CP, FA, and SSB pathways was 8.1%, 1.6%, 5.5%, 1.9%, and 0.0%, respectively.**
- **DDR-MT frequency was higher in right vs. left sided (20.9% vs 10.8%, p <0.001) and MSI-H vs. MSS (76.4% vs 9.5%, p <0.001) cases.**
- **In the MSS cases, right-sided had marginally higher frequency of DDR-MT than left-sided (10.6% vs 9.1%, p = 0.055), with much higher frequency of Fanconi anemia pathway alteration in right-sided (1.5% vs 0.7%, p<0.01).**
- **CMS1 subtype had the highest frequency of DDR-MT (34.8%); CMS2 had the lowest (7.1%).**
- **DDR-MT cases (vs. DDR-WT) had higher mutation rate of *ARID1A* (55.0% vs 19.1%, p<0.0001), *PIK3CA* (22.6% vs 15.8%, p<0.0001) and *BRAF* (20.4% vs 7.3%, p<0.0001), and lower mutation rate of *TP53* (48.2% vs 76.1%, p<0.0001), *APC* (60.5% vs 74.5%, p<0.0001) and *KRAS* (44.0% vs 49.8%, p<0.001).**
- **Mean TMB was much greater in DDR-MT than DDR-WT (All: 20.9/Mb vs 7.7/Mb, p<0.0001; MSS: 13.7/Mb vs 7.6/Mb, p<0.05). *PD-L1* positivity was also higher in DDR-MT compared to DDR-WT (All: 10.1% vs 2.7%, p<0.0001; MSS: 4.8% vs 2.4%, p<0.0001).**

Conclusions

- **Alteration of the DDR pathway was strongly associated with MSI status in CRC.**
- **DDR-MT was more prevalent in right-sided tumors compared to left-sided tumors.**
- **Elevated TMB and PD-L1 expression in DDR-MT CRC indicate more activated anti-tumor immune profiles compared to DDR-WT, regardless of MSI status, suggesting possible therapeutic benefit from immune checkpoint inhibitors in DDR-MT CRC.**

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