High endothelial venules are associated with hereditary background and immune evasion in microsatellite-unstable colorectal cancers

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InSIGHT Auckland 2019

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Conflicts of interest

I have no potential conflict of interest to report
Poster # 44
Board #14

Incident colorectal cancers in Lynch syndrome: mutational characteristics
Not all Lynch syndrome mutation carriers develop cancer
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Example: TGFBR2 A(10)

- slippage
- nucleotide sequence
- ATGAAAAGAAAAGCCCTGGTGAGA...TAG
  - MKEKKSLVR...
  - FSP neoantigen (34 aa)
- amino acid sequence

http://mythologian.net/ouroboros-symbol-of-infinity/
Evidence on different levels
Local and systemic immune responses in MSI CRC patients

Llosa et al. *Cancer Discov* 2014

Schwitalle et al. *Gastroenterology* 2008
Evidence on different levels:
Favorable prognosis of MSI CRC patients

Buckowitz *British J Cancer* 2005
Popat et al. *JCO* 2005

Le et al. *NEJM* 2015
Le et al. *Science* 2017
Host priming by MMR-deficient crypts
Lymphocyte recruitment by High Endothelial Venules (HEV)

Ager & May *Oncoimmunology* 2015
High Endothelial Venules (HEV)
Are HEVs involved in the immune response against Lynch syndrome tumors?
Lynch syndrome CRC have highest HEV counts
HEV counts and clinical parameters

**Age-based groups (years):**
- age ≤ 40: n = 14
- age 41–50: n = 17
- age 51–60: n = 28
- age 61–70: n = 24
- age ≥ 70: n = 33

**Age-independent cohort:**
- MSI hereditary: n = 20
- MSI sporadic: n = 20
- MSS: n = 20

**Tumor stage [UICC]:**
- UICC 1: n = 15
- UICC 2: n = 30
- UICC 3: n = 22
- UICC 4: n = 12
Selective pressure leads to impaired antigen presentation

Janikovits et al. *Oncoimmunology* 2017  
Echterdiek et al. *Oncoimmunology* 2015

Legend
- red: activated T cells
- green: regulatory T cells
- yellow: B2M-proficient tumor cells
- blue: B2M-mutant tumor cells
Lynch syndrome CRCs with lost antigen presentation have highest HEV counts
null
1) T cell priming by MMR-deficient crypt foci

- naive T cell
- FSP-specific T cell
- HEV
- cytokines
- MMR-proficient crypt
- MMR-deficient crypt
- MMR-deficient cell
- lysed B2M-wild type cell
- B2M-mutant MMR-deficient cell

Pfuderer et al. under review
Main messages

• MSI CRC show higher HEV densities than MSS CRC
• Among MSI CRC, Lynch syndrome CRC have the highest HEV counts
• Tumors with highest HEV counts are B2M-mutant
• HEV play an important role in tumor immunoediting in Lynch syndrome setting
Acknowledgements

Pauline Pfuderer
Ann Ager
Ian Frayling
Matthias Kloor
Alexej Ballhausen
Magnus von Knebel Doeberitz