Role of microsatellite instability in the oncogenesis of primary intestinal T-cell lymphomas

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INTRODUCTION

- Primary intestinal T-cell lymphomas (ITCL), which include monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL) and enteropathy-associated T-cell lymphoma (EATL) are a group of rare and aggressive extranodal lymphomas for which there is a limited range of treatments available.
- The presence of microsatellite instability (MSI) could represent a predictive factor for immunotherapy.

OBJECTIVE

To assess prevalence of MSI in ITCL and possible underlying molecular mechanisms.

DESIGN

- **Whole Exome Sequencing (WES) :**

  63 ITCL :
  - ✓ 37 MEITL
  - ✓ 26 EATL
- **Mismatch repair deficiency (MMRd) by immunohistochemistry (IHC)**

MLH1, MSH2, MSH6, PMS2 IHC
Automated BenchMark ULTRA platform (Ventana Tucson, AZ, USA)

58 ITCL

42 MEITL — 16 EATL

- **MSI status by PCR and fragment analysis** (using 5 well-established mononucleotide repeat markers) :

  43 ITCL :
  - ✓ 28 MEITL
  - ✓ 15 EATL

RESULTS

- Based on mutational profile, 3/37 MEITL (8%) (cases 001, 030 and 054) showed MSI-associated signatures and highest tumor mutational burden (TMB) among MEITL (highest TMB : 15 mutations/Mb) (**Figure 1 and 2**).
- Their MSI-high status was confirmed by PCR analyses (3/3), while the other 40/43 MEITL and EATL were microsatellite stable.
- MSI cases showed complete loss of PMS2 (case 054) or MLH1&PMS2 (cases 001 and 030) protein expression (**Figure 3**).

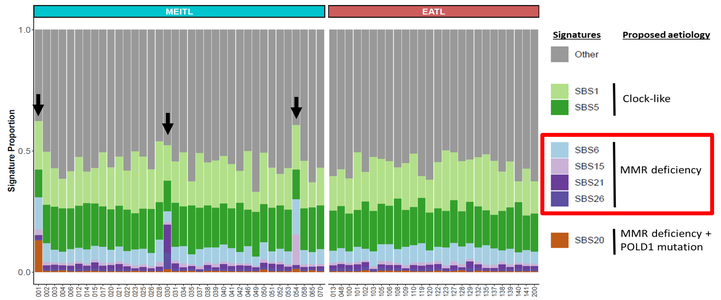


Figure 1 : MSI/MMRd-associated signatures by WES in MEITL 001, 030 and 054

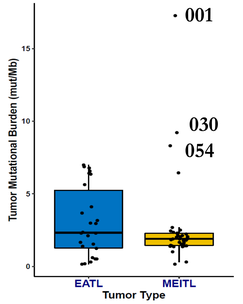


Figure 2 : TMB in ITCL

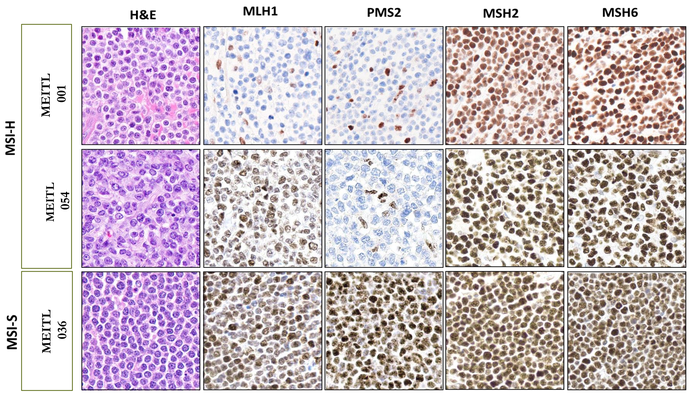


Figure 3 : MMRd by IHC in MEITL

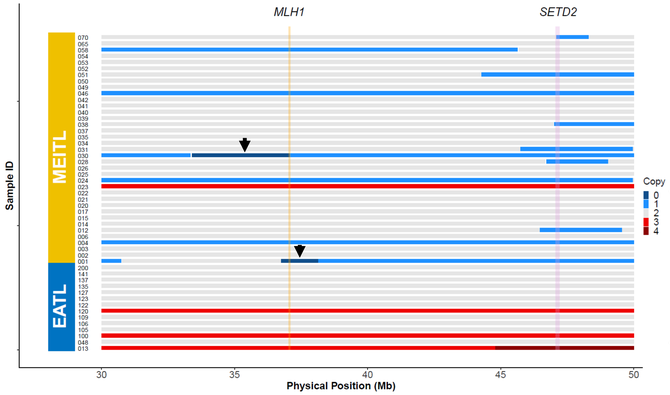


Figure 4 : *MLH1* CNV by WES in ITCL

- Notably, MSI tumors showed either biallelic deletion of the *MLH1* locus (patients with double MLH1 & PMS2 expression loss, cases 001 and 030) (**Figure 4**, arrows) or *PMS2* locus (patient with isolated loss of PMS2 expression, case 054).
- Further 2/42 MEITL (5%), MEITL 024 et 058 exhibited heterogeneous expression of MLH1 or MLH1&PMS2, associated with the loss of one copy of the *MLH1* locus.
- Finally, none of the tumors (0/63 WES) presented germline or somatic mutations of *MLH1, PMS2, MSH2 or MSH6*.

CONCLUSIONS

- MSI plays a role in the oncogenesis of a subset of ITCL, particularly MEITL, with potential therapeutic implications.
- In this series of ITCL, MSI and MMRd were related to *MLH1* or *PMS2* locus deletions.

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