The co-mutations and genetic features of \textit{BRAF}-mutated gene mutations in a large Chinese MSS colorectal cancer cohort

Sici Chen\textsuperscript{1}, Zeying Su\textsuperscript{1}, Shuizhi Ma\textsuperscript{1}, Zihao Sun\textsuperscript{1}, Xinyi Liu\textsuperscript{2}, Mengli Huang\textsuperscript{2}

\textsuperscript{1}Department of Oncology, First Affiliated Hospital of Guangdong Pharmaceutical University, Guangzhou 510080, China
\textsuperscript{2}Department of Medical, 3D Medicines Inc., Shanghai, China

Background

\textbf{BRAF} p.V600E is a known prognostic factor for poor progression-free survival and overall survival in colorectal cancer, occurring in 5\%-8\% patients. This is a special population resistance to chemotherapies. A combined regimen of targeted drugs including MEK inhibitor, \textit{BRAF} inhibitor and EGFR inhibitor is effective in \textit{BRAF} V600E mutated patients, while it only authorized as second-line treatment. \textit{BRAF} V600E mutation was also considered correlated with sporadic MSI-H. However, studies on other alterations in \textit{BRAF} gene are few, and the differences of comprehensive genetic features between \textit{BRAF} mutated and \textit{BRAF} wild-type in microsatellite stable (MSS) patients remain unclear.

Methods

A total of 6521 CRC with detected genomic amplifications were included in this analysis. Calling of single nucleotide variants (SNV), copy number variants (CNV), insertion/deletions (indels), fusions were performed using a wide panel next-generation sequencing (NGS) testing. SNV and indels in \textit{BRAF} gene excluding p.V600E were defined as other \textit{BRAF} mutations.

Results

316 (4.85\%) patients had \textit{BRAF} V600E alteration (V600E group), 243 (3.73\%) patients were detected to have other \textit{BRAF} mutations (\textit{BRAF other} group) and the rest was \textit{BRAF} wild-type (5962, 91.43\%). V600E and other \textit{BRAF} mutations occurred mutually exclusively (Figure 1).

The V600E group had significant higher somatic mutational rate in SMAD4 (26.6\% vs 17.3\% vs 14.9\%) and RNF43 (16.1\% vs 2.9\% vs 2.4\%) genes and lower mutational rate in APC (15.5\% vs 54.7\% vs 63.9\%) gene compared with the \textit{BRAF other} group and \textit{BRAF} wild-type group. The most recurrent amplified gene in V600E group was MYC (7\% vs 3.29\% vs 5\%), while another important gene in 8q24, PTK2 was amplified most in \textit{BRAF other} group (2.5\% vs 2.8\% vs 3.7\%).

As for tumor mutational burden (TMB) levels, the other \textit{BRAF} group had much higher TMB levels (median TMB level in the V600E group, the other \textit{BRAF} group and \textit{BRAF} wild-type group were 7.76 vs 59.4 vs 9.91) and significant correlated with hypermutation (>80 Muts/Mb), while no one hypermutation case was found in the V600E group (Figure 2).

Conclusion

The mutational rates of \textit{BRAF} V600E and other \textit{BRAF} mutations were approximate in MSS colorectal cancer. But the two groups had very different somatic genomic characteristics and very different correlations with hypermutation.