Comment on ‘Distinct clinical outcomes of two CIMP-positive colorectal cancer subtypes based on a revised CIMP classification system’

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Sir,

We read with interest the article by Bae et al (2017), where they proposed a revised CpG island methylator phenotype (CIMP) classification system for colorectal cancer (CRC) based on the methylation level, which was found to correlate with molecular alterations and the corresponding prognostic implications of CIMP-positive CRCs. They categorised CIMP-positive CRCs as CIMP-P1 or CIMP-P2 based on the number of methylated markers to better associate with clinicopathological and molecular features. Moreover, they have also underlined that CIMP-P1 CRCs should be more aggressive than CIMP-N and CIMP-P2 CRCs. They analysed a total of 1370 CRC patients for this new revised CIMP classification (Bae et al, 2017).

Since a few years ago, we are trying to characterise specific subgroups within CRC, some of them according to the age of onset of the disease, and others focusing on the development of multiple primary tumours. To date, these subset subgroups appear to be different in comparison with others CRCs (Kirzin et al, 2014; Lam, Chan and Leung, 2014; Pajares and Perea, 2015; Arriba et al, 2017). We have confirmed this finding, studying clinicopathological, familial and molecular points of view, and compared all the features found between those groups and with other sporadic CRC subsets.

Taking as the starting point the work by Bae et al (2017), we have analysed the same aspects described in their work, but differentiating patients with early-onset CRC (EOCRC; younger than 45 years), patients with late-onset CRC (LOCRC; older than 70 years), and individuals diagnosed with synchronous CRC (SCRC), that did not encompass cases with late-onset CRC (LOCRC; older than 70 years), and individuals diagnosed with synchronous CRC (SCRC). In this direction, LOCRC seems to be the most comparable subset to the results showed by Bae et al (2017). Maybe this could explain the difficulty of achieving a consensus about CIMP classification and the correlation with clinical and molecular phenotypes (Ogino et al, 2009; Lee et al, 2017).

With their refined CIMP classification system, CRCs from 1287 (93.9%), 62 (4.6%) and 21 (1.5%) patients were classified as CIMP-N, CIMP-P1 and CIMP-P2, respectively. In our three CRC subsets, EOCRC appeared to have the most similar proportions: 84%, 10% and 6%, respectively. LOCRC showed slight differences, with 74%, 17% and 9%, respectively. Finally, on the contrary appeared SCRC cases, with 37%, 4% and 18%; the other 41% arose for the CIMP-MM (Mismatch), where the tumours within the same patient show different CIMP status, as previously described (Arriba et al, 2017). Bae et al (2017) also tested the correlation between this revised CIMP classification and the pathological and molecular features. They associated patients with CIMP-P1 CRCs with proximal location, more advanced stage, poorly differentiated tumour and greater mucin production, compared with CIMP-N. In addition, CIMP-P2 CRCs showed some of those differential features as well (e.g., mucin production and proximal colon location; Bae et al, 2017). Some conclusion should be given according to the clinical and molecular features associated with CIMP categories, when we analysed our different age-of-onset groups and SCRC. In relation with EOCRC, patients with CIMP-P1 and CIMP-P2 CRCs showed higher proportions of proximal location (P = 0.013). Rendering familial cancer history, while CIMP-P1 were mainly sporadic cases, CIMP-N showed some predisposition for familial cancer aggregation, and CIMP-P2 mainly fulfilled Amsterdam criteria for Lynch syndrome. MLH1 methylation was mainstream in this last category. In the case of LOCRC, patients with CIMP-P1 CRCs were associated with the same molecular features described by Bae et al (2017; BRAF mutations, MSI cases and high MLH1 methylation). Results for patients diagnosed with SCRC showed that CIMP positive groups (CIMP-P1, CIMP-P2 and CIMP-MM) showed more MLH1 methylation than CIMP-N (p < 0.0001).

The findings shown by Bae et al (2017) according to the prognostic criteria, as age-of-onset or multiple primary neoplasms, when analysing CRC in this direction, LOCRC seems to be the most comparable subset to the results showed by Bae et al (2017). Maybe this could explain the difficulty of achieving a consensus about CIMP classification and the correlation with clinical and molecular phenotypes.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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