Up-regulation of c-Cbl suggests its potential role as oncogene in primary colorectal cancer

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Dear Editor:

Although progressive advances in early detection has been carried out in the last years, colorectal cancer (CRC) still represents the third cause of cancer death worldwide. This is because more than half of the patients progress to metastatic disease, which determines a very poor outcome. Therefore, it remains necessary to better understand the molecular basis that governs the progression from the early stages of CRC to metastatic development. In this context, the acquisition of invasiveness properties is a key molecular event that determines the progression from primary tumor to metastasis.

Of importance, it has been recently reported that c-Cbl, an E3 ubiquitin ligase and a multifunctional adaptor protein, regulates invasion ability of cancer cells through matrix metalloproteinase 2. It is an unexpected observation since c-Cbl was largely reported to play a tumor suppressor role in several tumor types. However, in concordance with this novel-proposed oncogenic role as regulator of cell adhesion, migration, and degradation, c-Cbl has been described as a marker of poor clinical outcome in prostate cancer. Therefore, it seems that this protein could be playing a dual role as a tumor suppressor or oncogene depending on the cancer model and stage of the disease. This novel-reported function for c-Cbl and the fact that its role in CRC remains unclear prompted us to analyze c-Cbl expression by western blot in a series of seven CRC cell lines. Interestingly, we observed increased

c-Cbl levels in the DLD-1, RKO, LoVo, and SW620 cell lines whereas the WiDr, SW480, and HT-29 cell lines showed a c-Cbl expression similar to normal colonic mucosa.

To further evaluate the importance of in CRC, we studied c-Cbl expression levels in 22 patients with primary CRC. Primary colorectal tissues were surgical resection specimens from CRC tumors obtained from Fundacion Jimenez Diaz Biobank (BFJD, Madrid). Tumor, node, metastases (TNM) staging was classified using the 7th American Joint Committee on Cancer (AJCC) staging system for colorectal cancer. Clinical data were collected from medical clinical records by an oncologist (J. G.-F.). Paired normal mucosa obtained from each patient was used as control. Moreover, a pathologist confirmed that primary tumor tissues used in this work contained greater than 70 % tumoral component (F. R.). All samples were taken anonymously and the ethical committee and institutional review board approved the project. Importantly, we found that 8 out of the 22 CRC cases showed c-Cbl overexpression in the tumor samples compared to their paired normal colonic mucosa. These results confirmed the previous observations made in CRC cell lines.

Altogether, our findings suggest that c-Cbl deregulation is a recurrent event that could be playing a role in the acquisition of invasiveness properties of CRC cells and might serve as a novel potential therapeutic target in a subset of CRC patients. However, further studies are needed to clarify this potential role of c-Cbl as oncogene in primary colorectal cancer and to determine its biological and clinical significance in the pathogenesis of this disease.

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