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Commentary

USP11 role in colorectal cancer growing and metastatisation

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Colo-Rectal Cancer (CRC) represents the third cause of cancer related death worldwide [1]. In the early stages (I-III) the approaches available for CRC treatment were represented by surgery followed or anticipated by chemo-radiotherapy. Unfortunately, a 20–25% of patients were diagnosed in advanced stages (IIIB-IV). In the past, for these patients the only therapeutic approach available was represented by chemotherapy. To date, technological innovation and the novel targeted therapies, such as antibodies against epidermal growth factor receptor (EGFR), showed their efficacy in a percentage of patients (about 50–60%) without mutation in *RAS* genes (*KRAS*, *NRAS*) and *BRAF* [2]. For this reason, a large part of metastatic CRC mCRC patients did not benefit of these fascinating therapeutic choice. In this setting, a better knowledge of the molecular mechanisms that could lead cancer development and survival represent an investigational hot – topic. Overall, there is a relevant unmet need in metastatic CRC (mCRC) patients with a constitute activation of MAPK pathway, due to the lack of target therapies for mCRC patients in this setting.

In this article of *EBioMedicine*, Sun and colleagues focused their attention on the role of ubiquitin-specific peptidase 11 (USP11) [3], a ubiquitin specific protease, in colo-rectal cancer (CRC) growth and metastasis through the activation of ERK/MAPK signaling pathway *via* PPP1CA-mediated activation [4]. They showed that USP11 played a key role in cancer progression due to the stabilization of PPP1CA. This latter, a serine-threonine phosphatases, is involved in ERK/MAPK signaling pathway activation [5]. The activation of this pathway induces tumor development [6,7]. For this reason, USP11 could represent a possible molecular target for tailored treatment of CRC patients.

Ubiquitination and de-ubiquitination represent relevant regulatory processes involved in protein homeostasis in several types of biological events [8]. A deregulation in these two factors, in particular the deregulation in deubiquitinating enzymes showed a relevant role in cancer progression [4]. As underlined by Sun *et al*, an overexpression of USP11 promoted cancer development *via* a constitutive activation of this pathway. The Authors showed, at either protein (with an immunoistochemical approach) or mRNA (RT-qPCR) levels, the high concentration of this protein in cancer tissue respect to the normal one. Subsequently, they demonstrated that the USP11 expression inhibition in cell lines was related to reduction of cell proliferation, migration, invasion and lead to an increasing cell death. Another level of investigation was related to *in vivo* models. In this setting, Sun and colleagues evaluate USP11 correlation with cell proliferation and tumorigenesis in xenograft models. Also in this case, as showed for cell lines, transfection of shUSP11 plasmids evidenced a smaller tumor volume respect to control mice. Literature data suggested that USP11 acts by inhibiting the apoptotic process in tumor cells [9]. Conversely, the Authors showed that USP11 did not affect the apoptotic way but influenced proliferation and cell growth by activating the ERK/MAPK signaling pathway. This evidence may be directly related to poor prognosis and a high level of liver metastasis [10].

Noteworthy, several issues influence the CRC development. In particular, we have not complete information about tumor complexity. Different gene alterations, genetic changes and modifications at epigenetic level should be better understand to define the scenario of CRC, in order to delineate the possible therapeutic choices. In addition, is still necessary correlate the role of USP11 with other gene mutations that may facilitate cancer development and progression. In this study the authors focalized the attention on the expression level of USP11 either at protein or RNA level. Further investigations are needed to better understand the presence of different gene alterations that could affect *USP11* gene function. The identification of hot-spots regions could influence protein function and structure, modifying its cancer related function, and the possibility to design a specific target drug. On the overall, it should be further investigated a cluster of patients with specific clinic-pathological features in which USP11 is more frequent, in order to better select patients for specific treatments. Another unmet need is represented by the prognostic role of USP11 overexpression and mutations need to be clarified in future studies involving a large number of patients.

The findings reported in this interesting paper add to our knowledge relevant data to better understand the relationship between USP11 deregulation and CRC development and the role of this pathway as a remarkable biomarker for mCRC patient's selection in the landscape of personalized therapy represents. Prospective and randomized clinical trials evaluating USP11 inhibitor molecules in CRC patients are welcomed.

Author's contribution

Umberto Malapelle wrote the commentary.

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Declaration of Competing Interest

Umberto Malapelle reports a consulting or advisory role for Boehringer Ingelheim, MSD, AstraZeneca, and Roche.

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