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Letter to the Editor

Comment on: "Formyl peptide receptor 2 mediated chemo-therapeutics drug resistance in colon cancer cells"

Dear Editor,

According to the epidemiology, colorectal cancer (CRC) is probably the most relevant enemy of oncologists in the Western world because it is the most commonly diagnosed neoplasm and, at the same time, the second leading cause of death among cancer patients[1].

Improvements in the surgical approach[2], in radiotherapy procedures[3], as well as recent implementations in pharmacological treatments, ranging from a more accurate dosing[4,5] and programming[6] of treatments with standard cytotoxic agents, to the integration of target therapies (which mainly concern the EGF/EGFR axis), led to doubling the life expectancy of patients with CRC, even in the metastatic phase of the disease[7].

However, as attested by clinical practice, the expectations of substantially changing the course of advanced stages of the disease with anti-angiogenic drugs, have been betrayed; therefore, in most of the cases, the common cytotoxic treatments remain the standard of care in the management of CRC and, more generally, of other types of cancer. In this regard, the intrinsic toxicity of chemotherapies, which has a negative impact on the tolerability of care, as well as the frequent emergence of chemical resistance, at the beginning or during treatment, still represents two important challenges in the fight against the CRC.

In this scenario, we have recently witnessed an increase in scientific efforts aimed at identifying new molecular targets to be used for further improvements in the treatment of CRC or other types of tumors. In fact, it has become evident that the identification, characterization, and validation of molecules exclusively, predominantly, or variously expressed by cancerous tissues, may be useful for modifying the course of the disease under several aspects: 1) by improving accuracy in the prognostic stratification of patients based on the differential expression of these molecules through the different stages of the disease; 2) by allowing the engineering of new "targeted" pharmacological tools, less toxic and more effective in eliminating only the transformed cells; 3) by providing useful molecular clues to direct each patient towards the best treatment option according to the expression of reliable biomarkers, predictive of a selective or multidrug chemo resistance.

In fact, with regard to solid tumors, there are several experimental demonstrations that the differential expression of membrane receptors (for example growth factor-[8] or cytokine-receptors[9]) can be exploited for drug targeting or to improve prognostic and therapeutic algorithms. Unfortunately, only in some cases these studies have been translated into clinical use, and frequently, as demonstrated for those biomarkers currently used for laboratory diagnosis of CRC, have proved insufficient in predicting the prognosis in critical phases of the disease.

Given these premises, it is clear that the work by Su et al[10], which describes the expression of the formyl-peptide receptor 3 (FRP3) in CRC tissues and its potential correlation with chemo resistance, is to be considered of potential interest.

As main element of novelty contained in this article, the authors propose that, conversely to what already described for other members of the so-called FRP family of G protein-coupled receptors, FPR3 may be induced in colon cancer histological specimens, also affirming, by means of experiments on human colon cancer cell lines, that this receptor may enable an anti-apoptotic signaling that relies on the activation of the Akt pathway[10]. To this regard, it should be noted that a comprehensive revision of the literature focused onto this family of receptors, that beyond FPR3

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also includes FPR1 and 2[11], attests that their expression is mainly, if not exclusively, restricted to phagocytes (monocytes, dendritic cells, and neutrophils).

As regards their biological role, the ability to homo-/hetero-dimerize among the different members of the same family seems to be relevant in taking part to different stages of innate and adaptive immunity; indeed, they are capable of triggering activation and mobilization of different leukocyte subsets in response to a wide range of peptide ligands, such as those originating from proteolysis of annexin 1 (the Ac2-26 fragment) or heme-binding protein 1 (the so-called FL2 fragment)[12].

Despite of that, an increasing number of demonstrations are accumulating in the most recent literature, supporting the possibility that FPR proteins may be expressed also in other type of cells (for instance in epithelial cells), therefore corroborating their potential involvement in processes beyond inflammation. In particular, in line with the hypothesis proposed by Su et al[10], FPRs expression has been documented in gastric cancer[13], seemingly to affect tumor progression and survival by their ability to stimulate cell invasion.

More provocatively in respect of colon cancers onset and progression, which recognize chronic inflammatory insults amongst the possible causative events, Leoni et al[14] hypothesize an important role for FPR receptors. In fact, these authors propose FPRs as mediators of the cross-talk between microbiota, immune cells and colon mucosa, in the process of recovering from a break-down of the intestinal barrier consequent to inflammatory insults.

In conclusion, the studies confirming the exact topology, the underlying molecular mechanisms and the clinical outcomes of FPR3 expression in CRCs, are indispensable for validating and translating the observations reported by Su et al[10] into a clinical practice. However, it is possible to hypothesize that a recognized mechanistic role of FPR3 in CRCs would make this protein an excellent candidate for the development of therapies for those subjects with a poor prognosis due to the lack of valid therapeutic alternatives; in fact, it is possible to imagine two different scenarios: one in which the use of selective agonists would enhance the immunological clearance of the tumor by recruiting the effectors of the innate immunity; the other in which the use of specific antagonists would directly damage the tumor cells by impairing the anti-apoptotic pathways that support resistance to chemotherapy. Even in the worst-case scenario, in which the over-expression of FPR3 is confirmed in tumors endowed with antimetabolite chemo resistance (e.g. towards 5-FU), but without any functional role in supporting this phenotype, this molecule could be proposed as a biomarker to predict the response to chemotherapies.

Conflict of interest

The authors declare no conflicts of interest.

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