ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO OPEN CANCER HORIZONS

NEWS

## In the literature: June 2021

### GUT VASCULAR BARRIER IMPAIRMENT LEADS TO INTESTINAL BACTERIA DISSEMINATION AND COLORECTAL CANCER METASTASIS TO LIVER

Colon cancer progression from the primary site to locoregional lymph nodes and from them to distant metastasis is an evolutionary paradigm. However, colon cancer cells migrate to distant organs skipping the lymphatic system.[1] Out of the colon, distant metastases are promoted by a premetastatic niche (PMN) characterized by a protumorigenic microenvironment. The contribution of microbiota in this process has been highlighted in several works and a certain type of microbiome has also been linked to the development and progression of colorectal cancer (CRC). Indeed, there is evidence that primary colon cancer and paired liver metastases are colonized by identical bacteria.[2] It is still not clear, however, if the bacteria may also participate in metastasis formation and colonize distant organs before, after, or concomitantly to cancer cell spreading. In an interesting article recently published in *Cancer Cell*, Bertocchi et al.[3] described how alterations in the gut vascular barrier (GVB) could justify the presence of both metachronous and liver metastatic lesions skipping lymph node step invasion.

The GVB represents a border between the gut and the blood circulation. It can be damaged by several factors, however, such as particular dietary regimens that induce a relevant change in intestinal microbiota. The evaluation of the GVB damage and subsequent increased blood vessel permeability can be assessed by the increased plasma vesicle-associated protein-1 (PV-1), a blood vessel endothelial-specific transmembrane protein. In this interesting work, the authors demonstrated that the higher frequency of (PV-1)+ cells, was related to an increased blood vessel permeability in the primary tumor of CRC patients and consequently correlates with the development of metachronous distant metastases.

The evidence derived from an analysis *in silico* was subsequently confirmed in an independent validation cohort. Interestingly, it was found that those patients with a high level of PV-1 presented more bacteria infiltration in liver metastases. *In vivo*, it was confirmed that this microbiome triggered the development of metastatic lesions. The authors suggest that bacteria enter the tumor and modify the GVB, and then they migrate to the liver and foster the formation of a PMN which creates the soil for subsequent cancer cell seeding. According to their data, the gut microbiome plays a relevant role in this phenomenon. In particular, a strain of *Escherichia coli* (C17) could directly open the GVB, through a type III secretion system virulence factor (Virf)-dependent mechanism, translocating into the liver, where it could initiate the recruitment of immune cells contributing to PMN maturation and favoring metastases formation. The same strain (*E. coli* C17) could be detected in human CRC (both primary tumor and liver metastatic foci). This work also suggests that PV-1 could be used as a prognostic biomarker for distal metastases. Although further validation is needed, the authors argue that this mechanism of metastasis formation may also apply to other tumors and organs, such as lung cancer.

### TARGETING FIBROBLAST GROWTH FACTOR RECEPTOR BEYOND FUSIONS IN INTRAHEPATIC CHOLANGIOCARCINOMA: *FGFR2* EXTRACELLULAR DOMAIN IN-FRAME DELETIONS ALSO PREDICT SENSITIVITY TO FIBROBLAST GROWTH FACTOR RECEPTOR INHIBITORS

The genomic landscape of biliary tract cancer includes a variety of potentially druggable targets such as *FGFR2* fusions, *IDH1*, or *BRAF* mutations, mismatch repair deficiency, *HER2* (*ERB2*) amplification/mutation and *ALK*, *ROS1*, or *NTRK* translocations. Among those, *FGFR2* molecular alterations are particularly prevalent in intrahepatic cholangiocarcinomas (IHCCs) and 15% present *FGFR2* activating fusions, whereas only 3% have point mutations. *FGFR2* fusions typically result from chromosomal events that lead to an in-frame fusion between the 5′ portion of the *FGFR2* gene, and a partner variable gene. On a structural level, the *FGFR2* portion of the fusion gene retains the extracellular domain, as well as the kinase-domain, whereas the fusion partner contributes a dimerization signal, leading to constitutive, ligand-independent pathway activation. However, in contrast with fusions, point mutations were related with resistance to fibroblast growth factor receptor (FGFR) inhibitors in IHCC.

Pemigatinib, an ATP-competitive FGFR kinase inhibitor, recently became the first Food and Drug Administration (FDA)-approved targeted therapy for cholangiocarcinoma, specifically among patients with *FGFR2* fusions with an objective response rate of 35.5%.[4] Erdafitinib, a potent pan-FGFR inhibitor, induced objective responses in approximately 40% of patients with metastatic urothelial cancers harboring *FGFR3* mutations or *FGFR2/3* fusions and got also FDA approval.[5] Moreover, some other selective compounds have been shown to effectively block constitutively activated *FGFR1-4* fusions in several tumor types and are currently under development.[6]

In a very comprehensive next-generation sequencing study of 335 biliary tract tumors recently reported at Cancer Discovery and lead by investigators at Dana Farber Cancer Center, the identification of 5 patients harboring *FGFR2* extracellular domain in-frame deletions among 178 IHCCs

(2.7%) was made as an unexpected mechanism of *FGFR2* activation. The authors confirmed the importance of *FRFR2* extracellular domain 'in-frame' deletions as oncogenic drivers *in silico,* in cell line models and *in vivo* and showed the ability of some FRGR inhibitors to block these activating signals.[7]

Concerning clinical antitumor activity of FGFR inhibitors, partial responses were observed among these patients with *FGFR2* extracellular domain in-frame deletions, comparing favorably with those reported for the different FGFR inhibitors in patients with IHCCs harboring *FGFR2* fusions. These findings suggest that the degree of oncogenic addiction to FGFR2 may vary across these mutational contexts and support further clinical evaluation of FGFR inhibitors in patients with *FGFR2* extracellular domain in-frame deletions. These alterations were also identified in other tumor types, suggesting a potentially important new treatment opportunity for patients with IHCCs and other malignancies.

## GENOMIC PROFILE OF ADVANCED BREAST CANCER IN CIRCULATING TUMOR DNA

Molecular profiling of breast cancer has typically focused on the primary breast lesion. Metastases are clonally related to the primary tumor, sharing many of the driver mutations, but nonetheless have typically acquired additional variants not detectable in the primary lesion. Therefore, archival primary tumor tissue does not represent the full genomic profile of advanced disease. Commonly, metastatic disease has been characterized by tumor biopsy. However, tissue biopsies are limited to observe temporal tumor evolution and the presence of spatial heterogeneity. In this scenario, liquid biopsy provides not only a valuable tool for cancer diagnosis, but also, for earlier detection of relapse, monitoring the tumor evolution and a more comprehensive assessment of tumor heterogeneity.[8]

In an inspiring manuscript published in *Nature Communications,* Kingston et al. utilize the largest prospective circulating tumor DNA (ctDNA) genomic profiling study (plasmaMATCH) to identify substantial novel features of advanced breast cancer with ctDNA sequencing.[9,10] They demonstrate the ability of ctDNA analysis to dissect spatial heterogeneity and subclonal sampling. The authors show, in hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2−) breast cancer, divergent routes to endocrine resistance in individual patients, suggesting different mechanisms of metastatic resistance. In fact, they observe that *ESR1* mutations co-exist with mitogen-activated protein kinase (MAPK) pathway alterations, in particular in patients with polyclonal *ESR1* mutations, associated with poor overall survival. Interestingly, in prior studies with tumor tissue, these alterations were described as mutually exclusive with *ESR1* mutations.[11]

To complete this analysis, a number of new therapeutic potentials are proposed. For example, in HER2+ breast cancer, the identification of acquired *HER2* mutations suggests novel mechanisms of resistance to anti-HER2 blockade implying a potential treatment strategy for its reversal. They also detected some other infrequent alterations in breast cancer such as *BRAF* mutations or microsatellite instability, which are also targetable, respectively, with specific inhibitors or immune checkpoint blockade. In addition, they described the role of APOBEC mutational signature in subclonal mutations and its implication in endocrine therapy resistance. Thereby, in luminal *PIK3CA* mutant disease, 23% of patients had multiple *PIK3CA* mutations. This second mutation was frequently subclonal conferring the worse prognosis. This polyclonal nature of endocrine resistance likely substantially challenges attempts to treat endocrine resistance disease.

This study illustrates the substantial clinical and research potential of ctDNA analysis in defining clonal architecture in cancer, identifying subclonal resistance mutation, establishing patterns of clonal dominance, and characterizing the mutational processes that drive diversification of metastatic breast cancer.

V. Gambardella[1,2], L. Candia[1], M. Tapia[1], J. M. Cejalvo[1,2] & A. Cervantes[1,2]*

[1]*Department of Medical Oncology, Biomedical Research Institute INCLIVA, University of Valencia, Valencia;*
[2]*CIBERONC, Instituto de Salud Carlos III, Madrid, Spain*
(*E-mail: andres.cervantes@uv.es).

Available online xxx



https://doi.org/10.1016/j.esmoop.2021.100186

## FUNDING

This paper was supported by grants from the Instituto de Salud Carlos III [grant number PI18/01909] to AC. JMC was supported by RIO Hortega SEOM contract (no grant number). VG was supported by Rio Hortega contract [grant number CM18/00241] from the Instituto de Salud Carlos III.

## DISCLOSURE

AC declares institutional research funding from Genentech, Merck Serono, Bristol-Myers Squibb, Merck Sharp & Dohme, Roche, Beigene, Bayer, Servier, Lilly, Novartis, Takeda, Astellas, Takeda, and Fibrogen and advisory board or speaker fees from Angem, Merck Serono, Roche, Bayer, Servier, and Pierre Fabre in the last 5 years. All other authors have declared no conflicts of interest.

## REFERENCES

1. Naxerova K, Reiter JG, Brachtel E, et al. Origins of lymphatic and distant metastases in human colorectal cancer. *Science*. 2017;357:55-60.

2. Bullman S, Pedamallu CS, Sicinska E, et al. Analysis of Fusobacterium persistence and antibiotic response in colorectal cancer. *Science*. 2017;358:1443-1448.
3. Bertocchi A, Carloni S, Ravenda PS, et al. Gut vascular barrier impairment leads to intestinal bacteria dissemination and colorectal cancer metastasis to liver. *Cancer Cell*. 2021;39:708-724.
4. Abou-Alfa GK, Sahai V, Hollebecque A, et al. Pemigatinib for previously treated, locally advanced or metastatic cholangiocarcinoma: a multicentre, open-label, phase 2 study. *Lancet Oncol*. 2020;21(5):671-684.
5. Loriot Y, Necchi A, Park SH, et al. Erdafitinib in locally advanced or metastatic urothelial carcinoma. *N Engl J Med*. 2019;381:338-348.
6. Schuler M. Inhibiting fibroblast growth factor receptors in cancer: the next generation. *Ann Oncol*. 2020;31:1285-1286.
7. Cleary JM, Raghavan S, Wu Q, et al. FGFR2 extracellular domain in-frame deletions are therapeutically targetable genomic alterations that function as oncogenic drivers in cholangiocarcinoma. *Cancer Discov*. 2021. https://doi.org/10.1158/2159-8290.CD-20-1669.
8. Alix-Panabières C, Pantel K. Liquid biopsy: from discovery to clinical application. *Cancer Discov*. 2021;11:858-873.
9. Kingston B, Cutts RJ, Bye H, et al. Genomic profile of advanced breast cancer in circulating tumour DNA. *Nat Commun*. 2021;12:2423.
10. Turner NC, Kingston B, Kilburn LS, et al. Circulating tumour DNA analysis to direct therapy in advanced breast cancer (plasmaMATCH): a multicentre, multicohort, phase 2a, platform trial. *Lancet Oncol*. 2020;21:1296-1308.
11. Razavi P, Chang MT, Xu G, et al. The genomic landscape of endocrine-resistant advanced breast cancers. *Cancer Cell*. 2018;34:427-438.