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Commentary

IFNγ signaling response in peripheral blood monocytes: A new prognostic biomarker for breast cancer?

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In this article of *EBioMedicine* [1], Wang and colleagues have shown that IFNγ signaling responsiveness was decreased in peripheral blood monocytes (PBMs) isolated from treatment naive breast cancer (BC) patients that relapsed, compared to BC patients that did not relapse. This was assessed by evaluating the phosphorylation status of STAT1 in CD14$^+$/CD16$^{-/lo}$ monocytes upon *ex-vivo* treatment of peripheral blood mononuclear cells with IFNγ. Consequently, in an exploratory and validation cohort, relapse free survival (RFS) was significantly worse in BC patients with a lower IFNγ signaling responsiveness in PBMs. Therefore, this suggests that IFNγ signaling responsiveness in PBMs could be a novel prognostic biomarker for relapse in BC.

Monocytes are classified in the following populations: classical (CD14$^+$/CD16$^-$), non-classical (CD14$^-$/CD16$^+$) and intermediate monocytes (CD14$^+$/CD16^{low}) [2]. The results obtained by Wang et al. are specific for CD14$^+$/CD16$^{-/lo}$ classical/intermediate monocytes as IFNγ signaling in non-classical monocytes was similar in relapsed and non-relapsed patients. The authors also investigated the potential correlation between MRC1 and CD163 expression on PBMs, two markers of an M2-like phenotype and IFNγ signaling response in PBMs from BC patients, though did not observe any significant correlations. Nonetheless, as monocytes are considered a highly plastic cell population, evaluation of the functional consequences of defective IFNγ signaling in PBMs could shed more light on their potential immunosuppressive character and consequent role in tumor progression [2].

Classical monocytes can give rise to tumor associated macrophages (TAMs) and the presence of TAMs has a negative prognostic value in most cancers [2,3]. Hence, the IFNγ signaling responsiveness in classical PBMs might influence the tumor infiltration by macrophages. Indeed, Wang et al. noted an inverse correlation between the TAM infiltration and the IFNγ signaling responsiveness in PBMs in matching samples. Interestingly, an inverse correlation was also observed between IFNγ signaling responsiveness in PBMs and the CSF1R levels on PBMs. CSF1R signaling is an important driver for the recruitment of monocytes in tumors and their *in situ* proliferation [4]. This was confirmed by Wang and colleagues, who showed that CSF1R on PBMs correlated with TAM numbers in matched breast tumors.

This would suggest a model where defective IFNγ signaling in PBMs results in higher CSF1R levels on monocytes and a consequent increased recruitment of monocytes to the tumor microenvironment and/or enhanced differentiation into TAMs. Indeed, in monocytes treated with IFNγ, CSF1R levels were significantly decreased in a concentration dependent manner. Considering the important role of CSF1R in the differentiation of monocytes to M2-like macrophages and their pro-tumoral role [4], the lower IFNγ signaling in monocytes might also lead to an increase in M2-like TAMs in BC tumors. Importantly, the M1/M2 classification is a model that is unable to fully recapitulate the *in vivo* complexity of the distinct functional macrophages subpopulations that can be found in tumors. Recent single cell RNA-sequencing analysis revealed that pro-tumor markers (CD204, CD206, and CD163) were heterogeneously expressed and that M2 is not a distinct state [5]. Moreover, it is important to take into consideration that classical monocytes are not the only source for TAMs, and that a dual origin of TAMs encompassing bone-marrow derived monocytes and tissue-resident macrophages has been documented in several cancer types such as pancreatic ductal adenocarcinoma and glioblastoma [6]. Resident mammary tissue macrophages might hence also contribute to the TAM pool in BC, as was suggested in the MMTV-PyMT spontaneous murine BC model [7].

To understand the causal relationship between IFNγ signaling response in PBMs and BC prognosis, dedicated *in vitro* and *in vivo* studies should be performed. This will help to understand the biology behind this axis as well as to aid the development of IFNγ signaling in PBMs as prognostic biomarker. These studies should also shed light on the origin of the defective IFNγ signaling in monocytes from BC patients that relapsed as this remains an open question.

In the current publication, the patient population consisted of non-metastatic BC patients, with over 80% of the patients presenting a luminal ER$^+$ HER2$^-$ subtype. Therefore, further investigation

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will be required to understand if this is specific for the luminal subtype or can also be extended to other BC subtypes. Considering the omnipresent role of the immune system in cancer and IFNγ signaling as a key pathway in immune cell signaling, the question can also be raised if this could be applied to other cancer types. On the other hand, it would also be important to understand if other inflammatory diseases could also cause a similar change in PBM IFNγ signaling and hence potentially hamper its use as prognostic biomarker in cancer.

Another aspect studied by Wang et al. was the IFNγ signaling in PBMs after remission in comparison to relapsed patients. Even though the dataset is limited, these results indicate higher IFNγ signaling in patients in remission than relapsed patients, suggesting reversibility of the IFNγ signaling defect. This is an interesting finding and is in agreement with the results published by Hamm et al. showing that the monocyte gene signature aimed at detection of colorectal cancer was reversible in patients in remission [8]. Nonetheless, in an initial step, these results would need to be confirmed in a much larger dataset as the current results are rather preliminary. Once confirmed, this could be an important new tool allowing a closer follow-up of patient treatment and response and a faster decision making for patients not showing a reversion of their IFNγ signaling defect. When doing so, careful attention would have to be given though to the impact of the treatment on monocyte IFNγ signaling to prevent false positive or negative results due to a direct impact of the treatment on monocytes.

In conclusion, the current publication adds to the evidence that PBMs are educated by the tumor and not only show a differential transcriptomic profile as was previously described for renal cell carcinoma, colorectal, breast and endometrial cancer [8–10], but also a defective signaling response to IFNγ. Therefore, Wang et al. provide promising evidence that supports the continued research into the use of peripheral blood monocytes as a liquid biopsy strategy for cancer diagnosis, as prognostic or predictive biomarker or as biomarker for treatment guidance.

Declaration of Competing Interest

The authors declare no conflict of interest.

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