Commentary

IFN\(\gamma\) signaling response in peripheral blood monocytes: A new prognostic biomarker for breast cancer?

Sofie Deschoemaeker\(^a,b\), Damya Laoui\(^a,b,*\)

\(^a\) Laboratory of Cellular and Molecular Immunology, Vrije Universiteit Brussel, Brussels, Belgium
\(^b\) Laboratory of Myeloid Cell Immunology, VIB Center for Inflammation Research, Brussels, Belgium

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In this article of EBioMedicine [1], Wang and colleagues have shown that IFN\(\gamma\) 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\(^{-}\) monocytes upon ex-vivo treatment of peripheral blood mononuclear cells with IFN\(\gamma\). Consequently, in an exploratory and validation cohort, relapse free survival (RFS) was significantly worse in BC patients with a lower IFN\(\gamma\) signaling responsiveness in PBMs. Therefore, this suggests that IFN\(\gamma\) 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\(^{low}\) classical/intermediate monocytes as IFN\(\gamma\) 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 IFN\(\gamma\) signaling in 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 also contribute to the TAM pool in BC, as suggested in the MMTV-PyMT spontaneous murine BC model [7].

To understand the causal relationship between IFN\(\gamma\) 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 IFN\(\gamma\) signaling in PBMs as prognostic biomarker. These studies should also shed light on the origin of the defective IFN\(\gamma\) 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...
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 IFN$\gamma$ 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 IFN$\gamma$ signaling and hence potentially hamper its use as prognostic biomarker in cancer.

Another aspect studied by Wang et al. was the IFN$\gamma$ signaling in PBMs after remission in comparison to relapsed patients. Even though the dataset is limited, these results indicate higher IFN$\gamma$ signaling in patients in remission than relapsed patients, suggesting reversibility of the IFN$\gamma$ 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 reversal of their IFN$\gamma$ signaling defect. When doing so, careful attention would have to be given though to the impact of the treatment on monocyte IFN$\gamma$ 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 IFN$\gamma$. 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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