

AUTHOR'S VIEW

## Metabolic reprogramming of myeloid-derived suppressor cells (MDSC) in cancer

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### ABSTRACT

MDSC undergo metabolic reprogramming in the tumor resulting in an increased fatty acid  $\beta$  oxidation that supports their immunosuppressive functions. Fatty acid oxidation inhibitors, used to treat coronary disease, significantly delayed tumor growth and had a significantly increased antitumor effect when combined with adoptive cell therapy or low dose chemotherapy.

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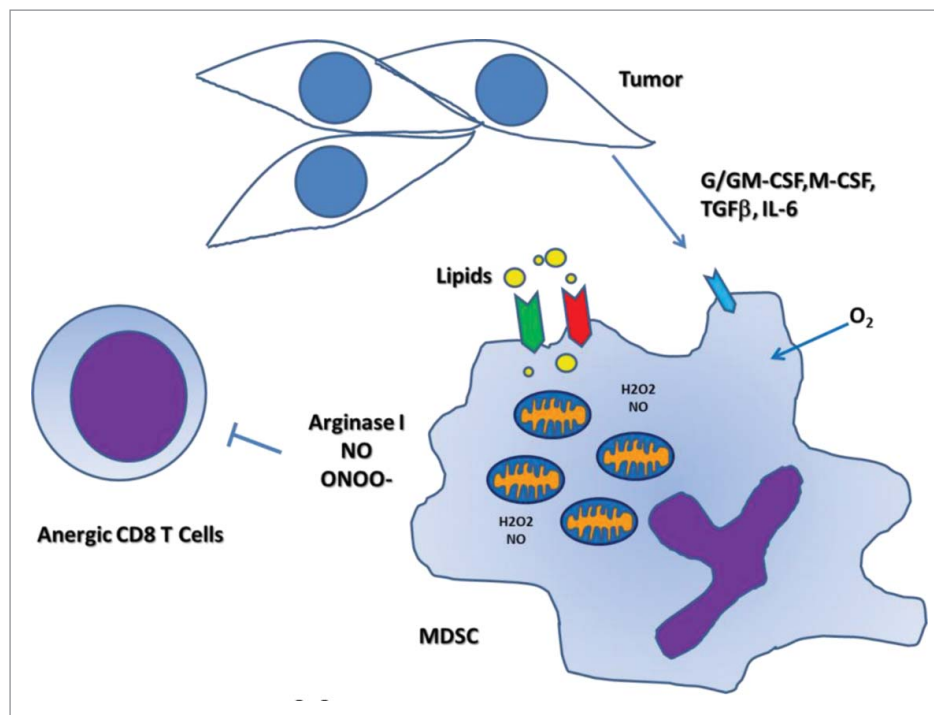
Myeloid cells normally play important roles in the initiation of protective immune responses and in the healing of damaged tissues. However, under the influence of tumor-derived factors (and certain chronic infections), they are hijacked to become myeloid-derived suppressor cells (MDSC) that inhibit antitumor T cell functions and protect tumors from the effects of chemotherapy and radiation therapy.<sup>1,2</sup> Inhibiting MDSC increases the efficacy of immunotherapy and/or radiation and chemotherapy. However, blocking MDSC has been difficult because they can respond to multiple tumor-derived factors, and they have at least three distinct mechanisms to block T cell function, namely the depletion of the amino-acids L-arginine (through arginase I) and L-cysteine, the production of nitric oxide (NO; through NOS2) and peroxynitrite (ONOO<sup>-</sup>; through the combined effect of NO + H<sub>2</sub>O<sub>2</sub>).<sup>3,4</sup> The plasticity of MDSC and the redundancy of their immunosuppressive mechanisms have made it difficult to inhibit them using targeted approaches such as arginase or nitric oxide inhibitors and tyrosine kinase inhibitors. Therefore, anti-MDSC therapies are mostly limited to high dose cyclophosphamide or gemcitabine, which block MDSC as a result of their myelosuppressive effects. Unfortunately, this results in a rapid increase in MDSC as the bone marrow recovers from the myelosuppressive effects of chemotherapy, reestablishing a highly immunosuppressive microenvironment.

During several decades, researchers have studied the energy metabolism of tumor cells with the goal of developing novel treatments of cancer.<sup>5,6</sup> More recently, several groups have studied the metabolic pathways used by immune cells at rest and after activation. The results have shown that different subpopulations have distinct metabolic requirements depending on their state of activation.<sup>7,8</sup> For example, resting CD8<sup>+</sup> T cells mostly use fatty acid oxidation (FAO) to maintain their “house

keeping” functions, but during their activation and effector stages they become highly glycolytic, finally returning to fatty acid oxidation when they develop into long-term memory cells. In contrast, CD4<sup>+</sup> CD25<sup>+</sup> FoxP3<sup>+</sup> regulatory T cells use FAO to support their immunosuppressive functions. Similarly, myeloid cells, as represented by macrophages and granulocytes, also have unique metabolic characteristics. While M1 macrophages and granulocytes preferentially use glycolysis, M2 macrophages primarily use FAO. In cancer, Gabrilovich's group showed that the synthesis and oxidation of lipids in CD11c<sup>+</sup> dendritic cells infiltrating tumors blocked the assembly of antigen onto Class II MHC and impaired antigen presentation, thus preventing the stimulation and activation of T cells.<sup>9</sup> This effect could be blocked if dendritic cells were treated with an inhibitor of fatty acid synthesis, TOFA.

As reported in our recent publication,<sup>10</sup> we studied the metabolic changes and characteristics of CD11b<sup>+</sup> GR1<sup>+</sup> MDSC (both Ly6G<sup>+</sup> granulocytic and Ly6C<sup>+</sup> monocytic MDSC). Normal granulocytes primarily use glycolysis to sustain their functions. Our results showed that tumor-associated MDSC, both granulocytic and monocytic, undergo metabolic reprogramming by significantly increasing fatty acid  $\beta$  oxidation. This metabolic reprogramming was characterized by an increased expression of the lipid uptake receptors CD36 and Msr1, an increase in the FAO enzymes carnitine palmitoyltransferase 1 (CPT1) and 3-hydroxyacyl-CoA dehydrogenase (HADHA), an increase in mitochondrial mass, and an increase in oxygen consumption rate. These events were paralleled with an activation of all three immunosuppressive mechanisms, namely an increased production of arginase I, an increased expression of NOS2 (together with NO production), and an increased production of ONOO<sup>-</sup>, which resulted in an enhanced ability to block T cell proliferation and IFN $\gamma$  production (Fig. 1).

We then tested the effect of FAO inhibition *in vitro* and *in vivo* using several transplantable tumor models. FAO inhibitors



**Figure 1.** Tumor-associated MDSC increase fatty acid uptake and activate FAO. Tumor-infiltrating MDSC show a heightened expression of lipid uptake receptors, such as CD36 and Msr1, thereby increasing fatty acid uptake. MDSC display an increased mitochondrial biogenesis and fatty acid oxidation. These events coincide with elevated immunosuppressive pathways, which block antitumor T cell responses.

developed to treat severe coronary disease (unstable angina) decreased the incorporation of fatty acids, decreased ATP production and blocked the development of all immunosuppressive functions of MDSC without causing apoptosis. Mice treated with FAO inhibitors had a significant decrease in tumor growth, which was dependent on CD4<sup>+</sup> and CD8<sup>+</sup> T cells. Furthermore, FAO inhibition enhanced the antitumor effect of single-dose chemotherapy and adoptive cellular therapy. The latter was accompanied by an increase in the number of CD8<sup>+</sup> T cells infiltrating the tumor and an increased production of IFN $\gamma$ . Therefore, targeting FAO may represent a new approach to globally inhibiting the function of tumor-associated MDSC without causing myelosuppression. It also appears to significantly enhance the effect of various forms of cancer therapy. These results support the need to continue understanding the metabolic reprogramming of immune cells in cancer and the possibility of using FAO inhibitors to potentiate the effect of immunotherapies, such as checkpoint inhibitors and adoptive cellular therapy, as well as standard cancer treatments, such as chemotherapy and radiation therapy. In addition, given its ability to modulate chronic inflammatory cells such as MDSC, it may be possible to use FAO inhibition as a way of treating other immune-mediated diseases.

### Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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