advisory role, Novartis, Pfizer, Inivata, and Sanofi-Aventis.

REFERENCES

Al-Khami, A.A., Zheng, L., Del Valle, L., Hossain, F., Wyczechowska, D., Zabaleta, J., Sanchez, M.D., Dean, M.J., Rodriguez, P.C., and Ochoa, A.C. (2017). Exogenous lipid uptake induces metabolic and functional reprogramming of tumor-associated myeloid-derived suppressor cells. OncoImmunology *6*, e1344804.

Baek, A.E., Yu, Y.A., He, S., Wardell, S.E., Chang, C.Y., Kwon, S., Pillai, R.V., McDowell, H.B., Thompson, J.W., Dubois, L.G., et al. (2017). The cholesterol metabolite 27 hydroxycholesterol facilitates breast cancer metastasis through its actions on immune cells. Nat. Commun. *8*, 864.

Bingle, L., Brown, N.J., and Lewis, C.E. (2002). The role of tumour-associated macrophages in tumour progression: implications for new anticancer therapies. J. Pathol. *196*, 254–265.

Christ, A., and Latz, E. (2019). The Western lifestyle has lasting effects on metaflammation. Nat. Rev. Immunol. *19*, 267–268.

Goossens, P., Rodriguez-Vita, J., Etzerodt, A., Masse, M., Rastoin, O., Gouirand, V., Ulas, T., Papantonopoulou, O., Van Eck, M., Auphan-Anezin, N., et al. (2019). Cholesterol efflux drives tumor-associated macrophage reprogramming and tumor progression. Cell Metab. *29*, this issue, 1376–1389.

Kuzu, O.F., Noory, M.A., and Robertson, G.P. (2016). The Role of cholesterol in cancer. Cancer Res. *76*, 2063–2070.

Nielsen, S.F., Nordestgaard, B.G., and Bojesen, S.E. (2013). Statin use and reduced cancer-related mortality. N. Engl. J. Med. *368*, 576–577.

Porta, C., Sica, A., and Riboldi, E. (2018). Tumor-associated myeloid cells: new understandings on their metabolic regulation and their influence in cancer immunotherapy. FEBS J. *285*, 717–733.

Pradel, L.C., Mitchell, A.J., Zarubica, A., Dufort, L., Chasson, L., Naquet, P., Broccardo, C., and Chimini, G. (2009). ATP-binding cassette transporter hallmarks tissue macrophages and modulates cytokine-triggered polarization programs. Eur. J. Immunol. *39*, 2270–2280.

Sag, D., Cekic, C., Wu, R., Linden, J., and Hedrick, C.C. (2015). The cholesterol transporter ABCG1 links cholesterol homeostasis and tumour immunity. Nat. Commun. *6*, 6354.

Strauss, L., Sangaletti, S., Consonni, F.M., Szebeni, G., Morlacchi, S., Totaro, M.G., Porta, C., Anselmo, A., Tartari, S., Doni, A., et al. (2015). RORC1 regulates tumor-promoting "emergency" granulo-monocytopoiesis. Cancer Cell *28*, 253–269.

Metabolic Adaptation Sets the Fate of Regulatory Macrophages

Jorge Domínguez-Andrés[1,2,*] and Mihai G. Netea[1,2,3,*]
[1]Department of Internal Medicine and Radboud Center for Infectious Diseases (RCI), Radboud University Nijmegen Medical Centre, Geert Grooteplein Zuid 8, 6525GA Nijmegen, the Netherlands
[2]Radboud Institute for Molecular Life Sciences, Radboud University Medical Center, 6525 GA Nijmegen, the Netherlands
[3]Department for Genomics & Immunoregulation, Life and Medical Sciences Institute (LIMES), University of Bonn, 53115 Bonn, Germany
*Correspondence: jorge.dominguezandres@radboudumc.nl (J.D.-A.), mihai.netea@radboudumc.nl (M.G.N.)
https://doi.org/10.1016/j.cmet.2019.05.012

In this issue of *Cell Metabolism*, Du et al. (2019) describe how insulin-like growth factor 2 (IGF-2), a protein with structural similarity to insulin, induces an anti-inflammatory phenotype in maturing macrophages through reprogramming of their mitochondrial metabolism. These anti-inflammatory properties are maintained upon secondary stimulation and alleviate experimental autoimmune encephalomyelitis (EAE) *in vivo*.

Macrophages have important roles for tissue repair and regeneration as well as host defense components against invading microorganisms. They are plastic cells that can differentiate and adapt toward specific phenotypes: a more proinflammatory phenotype is needed for host defense, whereas an anti-inflammatory or regulatory phenotype is necessary for the resolution of inflammation and tissue repair. These processes are under complex regulation. Much has been learned about the capacity of exogenous (especially microbial) and endogenous ligands to activate immunological, metabolic, and epigenetic pathways resulting in a proinflammatory phenotype (Lachmandas et al., 2016). However, much less is known about whether similar processes are also important for the induction of a regulatory phenotype of macrophages. In this issue of *Cell Metabolism*, Du, Lin, and colleagues take an important step toward understanding these processes by describing that insulin-like growth factor 2 (IGF-2), a protein hormone with structural similarity to insulin, induces a strong anti-inflammatory phenotype in maturing macrophages through reprogramming of their mitochondrial metabolism (Du et al., 2019). These anti-inflammatory properties are maintained upon secondary stimulation and alleviate experimental autoimmune encephalomyelitis (EAE) *in vivo*.

The immune system is constantly challenged by exogenous and endogenous stimuli. In recent years, it has been shown that not only lymphocytes but also myeloid cells from the innate immune system are able to "remember" the stimuli they encounter and undergo functional metabolic and epigenetic reprogramming, facilitating secondary inflammatory or anti-inflammatory responses upon restimulation (Netea et al., 2016). These innate immune memory mechanisms (also termed "trained immunity") were originally described to be triggered by microbial stimuli, such as LPS from Gram-negative bacteria or β-glucan from fungi, that respectively skew macrophages toward

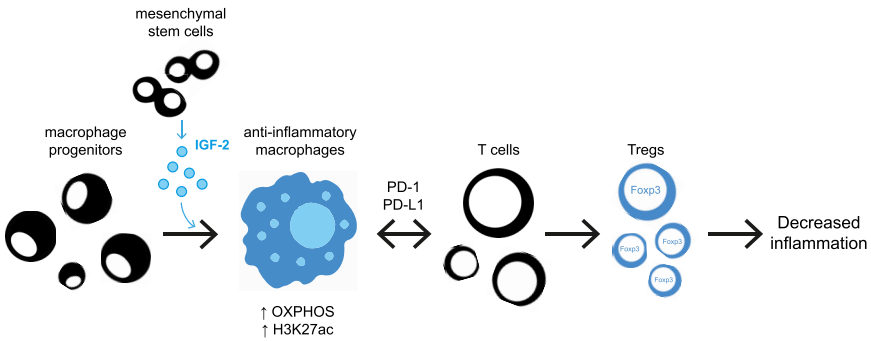

Figure 1. An IGF-2-PD-L1-Treg Axis Induces Anti-inflammatory Responses in Experimental Autoimmune Encephalomyelitis (EAE)

IGF-2 skews maturing macrophages toward an anti-inflammatory phenotype characterized by an OXPHOS-based metabolism, a changed landscape of H3K27ac marks, and an increased expression of PD-L1 on the surface. PD-L1 will bind PD-1 expressed on the surface of T cells, stimulating their differentiation toward T regulatory cells, which in turn decrease the inflammatory response in EAE.

an anti-inflammatory (tolerized) or pro-inflammatory (trained) phenotype. However, a growing number of reports have linked the functional and epigenetic reprogramming effects on myeloid cells with endogenous molecules such as TCA cycle metabolites (including succinate, fumarate, or itaconate), low-density lipoproteins, fatty acids, and amino acids (Domínguez-Andrés et al., 2019; Groh et al., 2018). In their elegant study, Du and colleagues describe how the blood circulating peptide IGF-2, mainly known for its growth factor activities during fetal development, commits the fate of maturing macrophages toward an anti-inflammatory phenotype (Figure 1).

When macrophage precursors are exposed to IGF-2 released from mesenchymal stem and/or stromal cells (MSCs), the activity of mitochondrial complex V markedly increases, committing the cells to a metabolism based on oxidative phosphorylation (OXPHOS). This metabolic rewiring of maturing macrophages is accompanied by epigenetic reprogramming, altering the distribution of H3K27ac marks in the genome of the differentiated macrophages. Therefore, the exposure of maturing macrophages to IGF-2 leads to both metabolic and epigenetic reprogramming of the cells, two hallmarks of the induction of innate immune memory (Figure 1). Very importantly, these effects are not observed if the macrophages are exposed to IGF-2 at a terminally differentiated stage, underlining the importance of these mechanisms in the context of cell differentiation and maturation. The increased anti-inflammatory activity of IGF-2-differentiated macrophages is related to an increased expression of Programmed Death-Ligand 1 (PD-L1). This higher levels of PD-L1 favor the differentiation of T cells into regulatory T (Treg) cells, ameliorating the responses to EAE *in vivo* in mice. Notably, direct treatment of mice with IGF-2 recapitulates this anti-inflammatory phenotype, highlighting the clinical potential of the mechanisms described and the differential effects of IGF-2 with respect to IGF-1, as the latter enhances the pro-inflammatory functions of macrophages (Bekkering et al., 2018).

The findings of Du et al. (2019) have important consequences for our understanding of macrophage biology. Macrophages have different origins during ontogeny, giving rise to functionally distinct subsets that are maintained during adulthood through mechanisms that are still to be elucidated. Macrophage polarization cannot be simplified to their ultimate pro- or anti-inflammatory properties. Macrophage polarization is a continuum, a whole spectrum of phenotypic markers, production of cytokines and chemokines, cytotoxic features, homeostatic activities, tissue repair, and wound healing activities, among many others (Atri et al., 2018). In addition, the pro-inflammatory activities of macrophages are also related to the development and complication of symptoms in inflammatory and autoimmune diseases such as (but not limited to) atherosclerosis, diabetes, asthma, rheumatoid arthritis, sepsis, and even certain types of cancers (Ponzoni et al., 2018). In such a complex scenario, it is fundamental to elucidate the epigenetic and metabolic mechanisms behind the modulation of the inflammatory responses in macrophages: on the one hand, this provides a crucial piece of the puzzle of macrophage regulation as a biological process, and on the other hand, this opens new avenues for the design of novel therapies.

It is probably in opening the door for new concepts in immunotherapy that the findings of Du et al. (2019) may prove to have the most important long-term consequences. Indeed, PD-1 and PD-L1 inhibitors are among the most promising agents in the developing field of cancer immunotherapy (Song et al., 2018). Du et al. (2019) suggest in their manuscript the existence of a strong link between the endogenous hormone IGF-2, mitochondrial metabolism, PD-L1 expression in macrophages, Treg cell differentiation, and inflammatory disease. First, induction of this novel pathway may represent a new approach for the treatment of autoimmune and autoinflammatory diseases, as the authors provide the proof-of-principle in a model of EAE. Second, inhibition of the IGF-2-PD-1-PD-L1 pathway may be hypothesized to be useful in cancer immunotherapy. Indeed, the current cancer immunotherapy is mainly targeting cytotoxic T cell function, while modulation of the IGF2-induced effects on macrophages may provide a complementary approach to modulate the phenotype of tumor-associated macrophages with pro-carcinogenic activities (TAMs) (Yang and Zhang, 2017) with potential beneficial effect. More efforts are required to decipher the extent of these effects, the associations behind the induction of innate and adaptive responses in the inflammatory context, and the best candidates for pharmacological targeting in various diseases.

In summary, Du, Lin, and colleagues describe a novel regulatory pathway involving IGF-2, mitochondrial complex V, and PD-L1 in maturing macrophages that can act as a key regulatory event in the context of cell polarization; they describe a new interplay between the endocrine system, epigenetics, metabolism, and innate and adaptive immune responses in the context of inflammatory diseases. More should be done in the future to understand the role of these processes in human diseases in order to realize the full biological and therapeutic potential of this discovery.

ACKNOWLEDGMENTS

M.G.N. was supported by a Spinoza grant of the Netherlands Organization for Scientific Research. We acknowledge Gorkem Oner for the icon "Dividing Stem Cells" from the Noun Project.

DECLARATION OF INTERESTS

M.G.N. is the scientific founder of Trained Therapeutics Discovery, a member of the Scientific Advisory Board of Inflazome, and has two patents related to therapeutic modulation of trained immunity.

REFERENCES

Atri, C., Guerfali, F.Z., and Laouini, D. (2018). Role of human macrophage polarization in inflammation during infectious diseases. Int. J. Mol. Sci. *19*, E1801.

Bekkering, S., Arts, R.J.W., Novakovic, B., Kourtzelis, I., van der Heijden, C.D.C.C., Li, Y., Popa, C.D., Ter Horst, R., van Tuijl, J., Netea-Maier, R.T., et al. (2018). Metabolic induction of trained immunity through the mevalonate pathway. Cell *172*, 135–146.e9.

Domínguez-Andrés, J., Novakovic, B., Li, Y., Scicluna, B.P., Gresnigt, M.S., Arts, R.J.W., Oosting, M., Moorlag, S.J.C.F.M., Groh, L.A., Zwaag, J., et al. (2019). The itaconate pathway is a central regulatory node linking innate immune tolerance and trained immunity. Cell Metab. *29*, 211–220.e5.

Du, L., Lin, L., Li, Q., Liu, K., Huang, Y., Wang, X., Cao, K., Chen, X., Cao, W., Li, F., et al. (2019). IGF-2 preprograms maturing macrophages to acquire oxidative phosphorylation-dependent anti-inflammatory properties. Cell Metab. *29*, this issue, 1363–1375.

Groh, L., Keating, S.T., Joosten, L.A.B., Netea, M.G., and Riksen, N.P. (2018). Monocyte and macrophage immunometabolism in atherosclerosis. Semin. Immunopathol. *40*, 203–214.

Lachmandas, E., Boutens, L., Ratter, J.M., Hijmans, A., Hooiveld, G.J., Joosten, L.A.B., Rodenburg, R.J., Fransen, J.A.M., Houtkooper, R.H., van Crevel, R., et al. (2016). Microbial stimulation of different Toll-like receptor signalling pathways induces diverse metabolic programmes in human monocytes. Nat. Microbiol. *2*, 16246.

Netea, M.G., Joosten, L.A.B., Latz, E., Mills, K.H.G., Natoli, G., Stunnenberg, H.G., ONeill, L.A.J., and Xavier, R.J. (2016). Trained immunity: a program of innate immune memory in health and disease. Science *352*, aaf1098.

Ponzoni, M., Pastorino, F., Di Paolo, D., Perri, P., and Brignole, C. (2018). Targeting macrophages as a potential therapeutic intervention: impact on inflammatory diseases and cancer. Int. J. Mol. Sci. *19*, E1953.

Song, M., Chen, X., Wang, L., and Zhang, Y. (2018). Future of anti-PD-1/PD-L1 applications: Combinations with other therapeutic regimens. Chin. J. Cancer Res. *30*, 157–172.

Yang, L., and Zhang, Y. (2017). Tumor-associated macrophages: from basic research to clinical application. J. Hematol. Oncol. *10*, 58.