



LETTER TO THE EDITOR

Redundancy in sarcoidosis granulomas



Dear editor,

I read the recently published research letter by Hindré et al. with great interest.¹ It describes a dramatic response to an mTOR inhibitor (sirolimus) in a patient with generalised sarcoidosis who after an initial marked response to JAK/STAT inhibitor (tofacitinib) showed a resistance to this drug. This case report is beautifully illustrated by a series of 18Fdg-PET-scan showing the active granulomatous lesions before and during tofacitinib and after sirolimus administration. It includes an interesting immunohistochemical (IHC) study focusing on the activation of JAK/STAT and mTOR pathways in dermal granulomas sampled before the tofacitinib treatment. No STAT1/3 phosphorylation indicative of an activated JAK/STAT pathway was clearly detected while the patient was responding to tofacitinib. This suggests that this granuloma may have been localised to a resistant area to skin lesions as shown on the second 18-FdG-PET-scan and that the JAK/STAT targets of tofacitinib were not expressed there, in contrast to other granulomatous lesions that initially respond. Another explanation could be an effect of tofacitinib on targets other than JAK/STAT, such as an inhibition of NOD2 expression, but this effect is thought to be more likely to inhibit the formation of new granulomas than to eradicate existing ones.² In contrast, the authors show that the mTOR pathway was already activated before tofacitinib treatment, for a better deciphering it would have been worth knowing if the sarcoid lesions were biopsied in an area refractory to tofacitinib treatment. Several pathways are known to be potentially activated and candidates for targeted treatment, initially reported for JAK/STAT, mTOR, NLRP3 and inflammasome.³ This observation suggests a heterogeneous cellular ecosystem in the different granulomas of the same patient, which is consistent with the observation that pulmonary granulomas have a rich CD4+ T-helper associated lymphocytic population in addition to monocytes-macrophages, the basic component of granulomas, whereas in the skin, naked granulomas with few associated lymphocytes are mostly observed. It also suggests a heterochrony in the activation of the different pathways in granulomas in

the same patient. Therefore, we can consider sarcoidosis lesions, as a complex system in which all potentially activated pathways are organised as redundant processes. Kraaijvanger et al. using IHC on a large set of sarcoid granulomas at diagnosis found concomitant activation of JAK/STAT, mTOR, NLRP3 in most granulomas with these activated pathways co-expressed in one third of the granulomas.⁴ If mTOR is found activated in most reports^{1,4,5} a heterogeneous association with cell cycle (Ki67 expression) was observed by Pizzini et al. suggesting a potential STAND-BY position for mTOR activation with a further step required to click on the ON position.⁵ It can be hypothesised that the various potentially activated pathways in granulomatous lesions may be in an ON, OFF or STAND-BY position and that resistance to an initially effective drug may be related to the activation of other redundant processes. Therefore, the granulomatous lesions of sarcoidosis should be studied using the most modern tools for analysing complexity before identifying driver pathways to be specifically targeted especially in each patient.

Conflicts of interest

The author has no conflicts of interest to declare.

References

- Hindré R, Besnard V, Kort F, Nunes H, Valeyre D, Jeny F. Complete response to mTOR inhibitor following JAKi failure in severe pulmonary sarcoidosis. *Pulmonology*. 2024. <https://doi.org/10.1016/j.pulmoe.2024.03.002>. Apr 13:S2531-0437(24)00042-4.
- Ueki Y, Takimoto-Ito R, Saito MK, Tanizaki H, Kambe N. Tofacitinib, a suppressor of NOD2 expression, is a potential treatment for Blau syndrome. *Front Immunol*. 2023;14:1211240. <https://doi.org/10.3389/fimmu.2023.1211240>.
- Riteau N, Bernaudin JF. In addition to mTOR and JAK/STAT, NLRP3 inflammasome is another key pathway activated in sarcoidosis. *Eur Respir J*. 2020;55:2000149. <https://doi.org/10.1183/13993003.00149-2020>.
- Kraaijvanger R, Ambarus CA, Damen J, van der Vis JJ, Kazemier KM, Grutters JC, et al. Simultaneous assessment of mTORC1, JAK/STAT, and NLRP3 inflammasome activation pathways in

<https://doi.org/10.1016/j.pulmoe.2024.05.001>

2531-0437/© 2024 Sociedade Portuguesa de Pneumologia. Published by Elsevier España, S.L.U. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

- patients with sarcoidosis. *Int J Mol Sci.* 2023;24:12792. <https://doi.org/10.3390/ijms241612792>.
5. Pizzini A, Bacher H, Aichner M, Franchi A, Watzinger K, Tancevski I, et al. High expression of mTOR signaling in granulomatous lesions is not predictive for the clinical course of sarcoidosis. *Respir Med.* 2021;177:106294. <https://doi.org/10.1016/j.rmed.2020.106294>.

J.-F. Bernaudin

Emeritus Professor of Histology & Cytology, Faculty of Medicine Sorbonne Université Paris, France

E-mail address: jf.bernaudin-univ@orange.fr

Received 1 May 2024; Accepted 9 May 2024

Available online 1 June 2024