Letter to Dermatology

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The Magnitude of mTORC1 Signalling May Predict the Response to Isotretinoin Treatment in Patients with Hidradenitis Suppurativa

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We have read with great interest the paper by Huang and Kirchhof [1] and the commentary by Boer [2]. Boer pointed out that the use of isotretinoin is not recommended by the European Treatment Guidelines for hidradenitis suppurativa (HS) [3]. Nevertheless, he noted that HS patients responding well to isotretinoin are the ones with inflammatory, migratory, furunculoid lesions [2].

In accordance with this view, we would like to provide our interpretation. We think that mechanistic target of rapamycin complex 1 (mTORC1) activity may determine the outcome to isotretinoin in patients with HS.

mTOR is the core constituent of the phosphatidylinositol 3-kinase-related kinase protein family that forms at least 2 multiprotein complexes known as mTORC1 and mTORC2 [4]. mTORC1 is the major regulator of survival, growth, proliferation, and motility in response to mitogen, energy, and nutrient levels [4]. Another important sensor of the cells' nutritional status is the forkhead box class O transcription factor-1 (FoxO1) [5]. FoxO1, also known as the transcription factor of starvation, inhibits the activity of mTORC1, thus linking nutrient availability to mTORC1-mediated protein and lipid synthesis, cell proliferation, and differentiation [5]. Due to its central role in cellular functions, mTORC1 dysregulation is involved in a number of inflammatory or neoplastic conditions [6]. The mTORC1 pathway is of pivotal importance for metabolic regulation and functioning of innate and adaptive immune cells, as clearly verified by the immunesuppressive function of mTORC1 inhibitors such as rapamycin [7]. Notably, the differentiation of Th17 cells is controlled by mTORC1, which promotes Th17 differentiation [8, 9]. Moran et al. [10] recently confirmed substantial infiltration of inflammatory Th17 cells with a striking Th17-skewed cytokine profile in HS skin. Upregulation of mTORC1 has been observed in common inflammatory IL-17-driven dermatoses such as psoriasis, acne vulgaris, and HS, respectively [11–13]. In particular, increased mTOR core protein expression has been found in lesional as well as non-lesional skin of HS patients [13], indicating exaggerated mTORC1 signalling in HS.

Substantial evidence has shown that isotretinoin increases nuclear levels of FoxO1 [14–17]. Recent evidence indicates that isotretinoin induces the expression of the transcription factor p53 [18, 19]. p53 induces the expression of FoxO1 and PTEN, but inhibits the expression of IGF-1 and androgen receptors, resulting in impaired IGF-1/mTORC1 and androgen signalling [19].

In light of the above, at least 2 considerations come to mind. Firstly, researchers often ask themselves why isotretinoin is not always effective in HS treatment. A possible explanation for its limited therapeutic response may be the fact that isotretinoin's major mode of action is p53-driven apoptosis [19]. Isotretinoin adversely affects the hair cycle and increases catagen, an apoptosis-dominated phase of the hair cycle [20, 21], which may further destabilize terminal hair follicles promoting HS, a dissecting terminal hair folliculitis [22].

On the other hand, we know from our experience with acne that isotretinoin reduces inflammation. From this perspective, isotretinoin-mediated downregulation of mTORC1 may attenuate the expression of mTORC1-induced production of IL-17, a proinflammatory signature cytokine overexpressed in HS lesions. Importantly, higher levels of mTOR expression can be detected in patients with inflammatory [13], especially migratory furunculoid, lesions [unpubl. data]. In the light of this evidence, it is arguable that patients exhibiting higher levels of mTORC1 activity may represent a subgroup in which isotretinoin-mediated suppression of mTORC1 exerts the most beneficial anti-inflammatory effects. On this subject matter, note that in HS mTOR gene expression statistically correlates with the severity of the disease and, like in acne vulgaris [23], with the body mass index (BMI) [13]. Recently, it has been suggested that patients with a low and high BMI could represent 2 clinically different subtypes, since eruption patterns and risk factors may change depending on the BMI value [24]. Consequently, isotretinoin might exert major anti-inflammatory effects in patients with a higher BMI.

To sum up, increased mTORC1 signalling in HS patients not only explains the association with other mTORC1-driven comorbidities including obesity [25], but also suggests a possible mechanism of action of isotretinoin in HS. In this regard, it should be mentioned that metformin, another inhibitor of mTORC1 [17, 26], improved acne [27] and HS [28], likely sharing a common mode of action with isotretinoin. The different magnitude of mTORC1 signalling in clinically different subtypes may explain and predict the different response to isotretinoin in patients with HS. Further laboratory and clinical investigations are required to increase our understanding of the complex interplay of metabolic deviations, immune regulation, and therapeutic intervention in HS.

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Key Message

HS patients who have higher levels of mTOR expression may represent an inflammation-prone subgroup who may exhibit a higher benefit from isotretinoin treatment.

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Disclosure Statement

The authors declare no conflict of interest. No financial interest exists.

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