Title

From FOS fusions to somatic mutations in the MAPK pathway, heterogeneous genetic abnormalities cause distinct pathophysiology among subsets of epithelioid haemangiomas

Journal

British Journal of Dermatology, 186(3)

ISSN

0007-0963

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Publication Date

2022-03-01

DOI

10.1111/bjd.20952

Peer reviewed

Conflicts of interest: the authors declare they have no conflicts of interest.

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From *FOS* fusions to somatic mutations in the MAPK pathway, heterogeneous genetic abnormalities cause distinct pathophysiology among subsets of epithelioid haemangiomas

DOI: 10.1111/bjd.20952

Linked Article: Maurus *et al.* *Br J Dermatol* 2022; **186**:553–563.

Epithelioid haemangioma (EH) is a rare benign vascular tumour comprised of prominent epithelioid endothelial cells, occurring at diverse anatomical locations including soft tissues, bone and skin.[1,2] EH can be categorized into three subsets: typical, cellular, and angiolymphoid hyperplasia with eosinophilia (ALHE), with a wide range of vasoproliferative spectra and inflammatory infiltrates. The emerging evidence of genetic abnormalities in EH includes *FOS* rearrangements and somatic mutations in the mitogen-activated protein kinase (MAPK) pathway. This has greatly enhanced our understanding of the aetiology of this disease and facilitated molecular differential diagnosis from malignant epithelioid vascular tumours such as epithelioid haemangioendothelioma and angiosarcoma.

There are several types of *FOS* gene fusions reported in EH, including *ZFP36/FOSB*, *WWTR1/FOSB*, *FOS/LMNA* and *FOS/VIM*, which lead to consecutive overexpression of their transcripts.[3–5] These *FOS* rearrangements are commonly found in soft tissue and intraosseous lesions, but are very infrequent in cutaneous EH.[3,6] In addition, a fusion of *GATA6/FOXO1* was reported in a subset of EH lacking *FOS* fusions.[7]

In this issue of the BJD, Maurus *et al.* report various somatic mutations in *MAP2K1* and *KRAS* in cutaneous EH, which resulted in an enhanced MAPK pathway.[8] These somatic mutations may account for distinct pathological mechanisms underlying the development of cutaneous EH where *FOS* gene fusions are absent. The authors identified several somatic mutations in the *MAP2K1* gene (including c.383G>A, p.Gly128Asp and c.171G>T or C, p.Lys57Asn) and in the *KRAS* gene (c.182A>G, p.Gln61Arg).[8] These mutations occur in 50% of patients across all three EH subsets: typical, cellular and ALHE. The mutation allele frequency ranged from 1·5% to 6·2%.[8] As a pathological readout of these mutations, a strong activation of the MAPK pathway and subsequently morphological changes in endothelial cells was observed.[8]

Low-frequency somatic mutations in many MAPK pathway-associated genes (*KRAS*, *NRAS*, *BRAF* and *MAP2K1*) have been reported in various vascular anomalies including arteriovenous malformations.[9] This cumulative evidence combined with the report from Maurus *et al.* suggests a mechanistic role of mosaic mutations for targeting the MAPK pathway in the pathogenesis of certain cutaneous vascular disorders including EH. However, there are several critical questions yet to be answered prior to affirmation of their detrimental roles. Firstly, are these low-frequency somatic mutations primary causes, role players or merely pathological consequences of the EH? Secondly, which cell types in lesions harbour those mutations? Maurus *et al.* suggest that epithelioid endothelial cells carry the mutations but lymphocytes do not.[8] As a result of the low frequencies of these mutations, it is reasonably posited that only a very few epithelioid endothelial cells carry the mutations. What are the molecular phenotypes of those mutation-harbouring cells and what are their detrimental roles in the development and progression of the cutaneous EH? Thirdly, if somatic mutations in the MAPK pathway act as a 'second hit' for cutaneous EH development, the 'primary hit' has yet to be elucidated.

Nevertheless, the identification of somatic mutations in *MAP2K1* and *KRAS* has provided a new insight into the neoplastic nature of cutaneous EH, suggesting various genetic abnormalities underlying distinct molecular pathophysiology among subsets of EH.

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Funding sources: this work was supported by a grant from the National Institutes of Health (AR073172 to W.T.).

Conflicts of interest: the authors declare they have no conflicts of interest.

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Safety in numbers: risankizumab for moderate-to-severe psoriasis

DOI: 10.1111/bjd.20947

Linked Article: Gordon *et al*. *Br J Dermatol* 2022; **186**:466–475.

Biologic therapies are effective at improving the quality of life and clinical outcomes of patients with moderate-to-severe psoriasis.[1] Risankizumab – a humanized monoclonal antibody that inhibits interleukin (IL)-23, a key cytokine in the pathogenesis of psoriasis – is effective for treatment of psoriasis and Crohn disease.[2–6]

In this issue of the *BJD*, Gordon *et al*. report on the safety of risankizumab by analysing data from 17 completed or ongoing trials in patients with plaque psoriasis.[7] Adverse events were reported as exposure-adjusted event rates (EAERs) per 100 patient-years (PY). The dataset was divided into adverse events that occurred in the short term (defined as <16 weeks; 1306 patients) and adverse events that occurred in the long term (3072 patients). Consistently with previous clinical trials, the most common adverse events were nasopharyngitis and viral upper respiratory tract infections (URTIs).[3–6] Most of the EAERs recorded were mild or moderate, with serious drug-related EAERs accounting for only 1·5 and 1·0 events per 100 PY in the short- and long-term datasets, respectively, in line with benchmark reference ranges.

Importantly, this study did not identify any new safety signals for risankizumab. Inhibition of IL-23 did not predispose patients to bacterial or fungal pathogens, nor did it increase the risk of malignancy. In head-to-head clinical trials with other biologics such as ustekinumab (anti-IL-12/23), adalimumab (anti-tumour necrosis factor) and secukinumab (anti-IL-17A), risankizumab was more effective in the treatment of moderate-to-severe plaque psoriasis and had a similar safety profile, with the most common adverse event being viral URTIs.[3–6] Based on the evidence we have so far, risankizumab appears to be both effective and safe.

While these findings are encouraging, there are several limitations to consider. Although the authors include comprehensive safety data from 17 clinical trials, the generalizability of the results is limited to the populations included in the original trials. For example, a reviewer noted that although the authors report very few cases of infections such as tuberculosis in patients treated with risankizumab, the majority of trials were conducted in countries with low rates of tuberculosis, making it unclear how these safety data might differ in countries with higher prevalence of tuberculosis.

As the authors acknowledge, patient attrition over time may have selected for healthier patients at later timepoints, potentially biasing the long-term safety profile of risankizumab. Safety data were available for over 5 years, making this the most comprehensive study on the safety of risankizumab to date; however, many of the safety concerns, including cancer, may take decades to develop, making it paramount to continue efforts to collect safety data in the long term. Data from large registries, such as BADBIR (British Association of Dermatologists Biologics and Immunomodulators Register), provide the power and duration of follow-up necessary to identify any rare or delayed adverse effects in a real-world setting.[8]

In summary, this study provides encouraging data for the safety profile of risankizumab for the management of moderate-to-severe plaque psoriasis. Continued analyses in real-world settings and ongoing clinical trials are necessary to further characterize the long-term side-effect profile of risankizumab in diverse settings, and to highlight the potential barriers to access to biologics and implications in the context of growing healthcare costs.[9]

Acknowledgments: We thank Dr Zenas Yiu, *BJD* Associate Editor and NIHR Clinical Lecturer at the University of Manchester, for his contribution to this commentary.

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Conflicts of interest: the authors declare they have no conflicts of interest.

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