As previously reported in European skin, Chen *et al.*[5] confirm an association for skin wrinkling with polymorphisms in the *IRF4*, *MC1R* and *SLC45A2* genes – indicating their conserved nature. However, they also identified two novel loci associated with the skin wrinkling trait, most notably *VAV3*, and a previously unreported association of mole count with *SLC45A2*, a gene well known to be involved in pigmentation and in melanoma susceptibility.[8]

Our current knowledge of genes contributing to differences in skin structure or responses to environmental stressors is scant. However, this paper is a great example of 'big team science', where collaboration across disparate scientific areas has produced a study that adds to our collective understanding of skin biology. In light of the skin's role as a key mediator of the body's interactions with the environment, there is every reason to believe that functionally significant variation exists in the genes determining skin ageing. Further studies examining human skin diversity should continue to be encouraged.

Acknowledgments: Thanks to Dr Mark Farrar (Centre for Dermatology Research, The University of Manchester) for his critical review of this commentary.

A. K. Langton [1,2,3] and R. E. B. Watson [1,2,3]

[1]*Centre for Dermatology Research, The University of Manchester & Salford Royal NHS Foundation Trust, Salford, Manchester Academic Health Science Centre, Manchester, UK;* [2]*Manchester Institute for Collaborative Research on Ageing, University of Manchester, Manchester, UK; and* [3]*NIHR Manchester Biomedical Research Centre, Manchester University NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, UK*
Email: abigail.langton@manchester.ac.uk

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

References

1 Jablonski NG. 'Ethnic skin' and why the study of human cutaneous diversity is important. *Br J Dermatol* 2013; **169** (Suppl. 3):v.
2 Del Bino S, Bernerd F. Variations in skin colour and the biological consequences of ultraviolet radiation exposure. *Br J Dermatol* 2013; **169**:33–40.
3 Ud-Din S, Bayat A. Strategic management of keloid disease in ethnic skin: a structured approach supported by the emerging literature. *Br J Dermatol* 2013; **169**:71–81.
4 Rawlings AV. Ethnic skin types: are there differences in skin structure and function? *Int J Cosmet Sci* 2006; **28**:79–93.
5 Chen F, André M, Adhikari K *et al.* A genome-wide association study identifies novel gene associations with facial skin wrinkling and mole count in Latin Americans. *Br J Dermatol* 2021; **185**:988–98.
6 Le Clerc S, Taing L, Ezzedine K *et al.* A genome-wide association study in Caucasian women points out a putative role of the *STXBP5L* gene in facial photoaging. *J Invest Dermatol* 2013; **133**:929–35.
7 Jacobs LC, Hamer MA, Gunn DA *et al.* A genome-wide association study identifies the skin color genes *IRF4*, *MC1R*, *ASIP*, and *BNC2* influencing facial pigmented spots. *J Invest Dermatol* 2015; **135**:1735–42.
8 Gandini S, Sera F, Cattaruzza MS *et al.* Meta-analysis of risk factors for cutaneous melanoma: I. Common and atypical naevi. *Eur J Cancer* 2005; **41**:28–44.

Mycosis fungoides-derived exosomes and their microRNA-1246 cargo: a message from the skin

DOI: 10.1111/bjd.20695

Linked Article: Moyal *et al.* Br J Dermatol 2021; **185**:999–1012.

Exosomes are small extracellular vesicles containing proteins, lipids and nucleic acids that facilitate cell–cell communication, influence local and distant microenvironments, and have implications in cancer pathogenesis. MicroRNAs (miRNAs), which act as key post-transcriptional regulators of gene expression, are an important part of the exosome content.[1,2] In recent years, evidence has accumulated that dysregulated miRNA expression interferes with tumour immunity and plays a crucial role in the pathogenesis of diverse malignancies including cutaneous T-cell lymphoma (CTCL).[2,3] While data addressing the role of exosomes in the most common CTCL, mycosis fungoides (MF), are only just increasing, some miRNAs have already caught attention as promising candidates for much needed diagnostic and prognostic biomarkers and novel therapeutic targets.[4,5,6]

In this issue of the *BJD*, Moyal and colleagues[7] elegantly implement transmission electron microscopy and nanoparticle tracking analysis to track the presence of tumour-derived exosomes in MF and to gain insights into their miRNA profile *in vitro* and *ex vivo*.[7] Besides demonstrating for the first time the existence of MF-derived exosomes, the study identifies miR-1246 as a major miRNA in the MF cell line exosomal content and confirms the importance of miR-155 in the pathogenesis of MF (Figure 1).

In general, miR-155 overexpression is one of the best characterized features of MF disease progression and is associated with increased cancer proliferation and tumour cell survival.[2,8,9] Based on this knowledge, a prospective phase II clinical trial already explores the efficacy of the anti-miR-155 compound Cobomarsen (MRG-106) in MF (https://clinicaltrials.gov/ct2/show/NCT03713320). Thus, the study of Moyal and colleagues provides further evidence for the general role of miR-155 in MF and especially its capacity to enhance cell migration of malignant MF cells.[7] Interestingly, both miR-155 and miR-1246 are present in MF cell line exosomes. However, in elucidating specifically the role of tumour-derived exosomal miRNAs (exomiRNAs), Moyal and colleagues[7] expand their research beyond *in vitro* cell-line data to *ex vivo* disease-stage dependent analysis of MF exosomes and

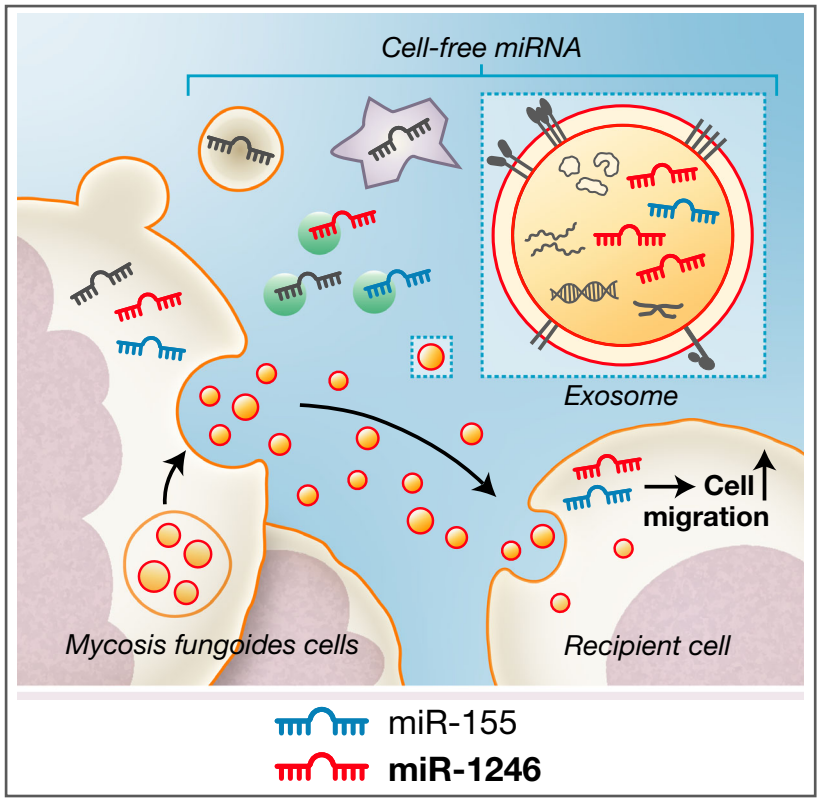

Fig 1 Route of mycosis fungoides (MF)-derived microRNA (miRNA). Formation of exosomes is one way for MF tumour cells to discharge their cell-free miRNA to the extracellular space. Besides proteins, lipids and nucleic acids, miR-155 and especially miR-1246 were identified as major cargo of MF-derived exosomes. After their release from MF cells, exosomes are incorporated by benign and malignant recipient cells of the immune system, which markedly increases the migratory capabilities of these cells. Exosomal miR-155 significantly contributes to this migratory effect.

their exomiRNA content in MF patient plasma. Of interest, in the plasma of 18 patients with advanced MF, manifesting clinically with plaque and tumour skin lesions, expression of exomiR-1246 but not exomiR-155 was significantly higher than in plasma of healthy individuals.[7] Regarding total circulating cell-free miRNA (cfmiRNA), plasma levels of both cfmiR-155 and cfmiR-1246 were higher in patients with advanced MF than in healthy individuals, notably independent of the patient's blood tumour burden.[7]

Collectively, while this novel study performed by Moyal and colleagues[7] does not yet fully explain the relevance of the MF-derived exomiRNA, the observations especially on cfmiRNAs do suggest a direct translational application in clinics. Both cfmiR-155 and cfmiR-1246, together with exomiR-1246, should be considered as MF-associated molecular biomarkers for advanced skin disease. They may play a role as novel therapeutic targets and open a perspective towards the development of diagnostic approaches such as liquid biopsy for CTCL.

Acknowledgments: the authors thank Wolfram Hoetzenecker (Department of Dermatology, Kepler University Hospital, Johannes Kepler University, Linz, Austria) and Curdin Conrad (Department of Dermatology, Lausanne University Hospital, Lausanne, Switzerland) for their critical review of this commentary. Open access funding provided by Universite de Lausanne.

I. Pospischil[1] and E. Guenova[2,3]

[1]Department of Dermatology, Kepler University Hospital, Johannes Kepler University, Linz, Austria; [2]Department of Dermatology, University Hospital Zurich and the University of Zurich, Zurich, Switzerland; and [3]Department of Dermatology, Lausanne University Hospital (CHUV) and the Faculty of Biology and Medicine, University of Lausanne, Lausanne, Switzerland

Correspondence: Emmanuella Guenova.
Email: emmanuella.guenova@unil.ch

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

References

1 Whiteside TL. Tumor-derived exosomes and their role in cancer progression. *Adv Clin Chem* 2016; **74**:103–41.
2 Gluud M, Willerslev-Olsen A, Gjerdrum LMR *et al*. MicroRNAs in the pathogenesis, diagnosis, prognosis and targeted treatment of cutaneous T-cell lymphomas. *Cancers (Basel)* 2020; **12**:1229.

3 Bobrowicz M, Fassnacht C, Ignatova D *et al*. Pathogenesis and therapy of primary cutaneous T-cell lymphoma: Collegium Internationale Allergologicum (CIA) update 2020. *Int Arch Allergy Immunol* 2020; **181**:733–45.
4 Dusilková N, Bašová P, Polivka J *et al*. Plasma miR-155, miR-203, and miR-205 are biomarkers for monitoring of primary cutaneous T-cell lymphomas. *Int J Mol Sci* 2017; **18**:2136.
5 Moyal L, Yehezkel S, Gorovitz B *et al*. Oncogenic role of microRNA-155 in mycosis fungoides: an *in vitro* and xenograft mouse model study. *Br J Dermatol* 2017; **177**:791–800.
6 Ralfkiaer U, Lindahl LM, Litman T *et al*. MicroRNA expression in early mycosis fungoides is distinctly different from atopic dermatitis and advanced cutaneous T-cell lymphoma. *Anticancer Res* 2014; **34**:7207–17.
7 Moyal L, Arkin C, Gorovitz-Haris B *et al*. Mycosis fungoides-derived exosomes promote cell motility and are enriched with microRNA-155 and microRNA-1246, and their plasma-cell-free expression may serve as a potential biomarker for disease burden. *Br J Dermatol* 2021; **185**:999–1012.
8 van Kester MS, Ballabio E, Benner MF *et al*. miRNA expression profiling of mycosis fungoides. *Mol Oncol* 2011; **5**:273–80.
9 Moyal L, Barzilai A, Gorovitz B *et al*. miR-155 is involved in tumor progression of mycosis fungoides. *Exp Dermatol* 2013; **22**:431–3.