Transcriptomic changes during stage progression of mycosis fungoides: from translational analyses to their potential clinical implications

DOI: 10.1111/bjd.20895

Linked Article: Xiao et al. Br J Dermatol 2022; 186:520–531.

Mycosis fungoides (MF) is the most frequent cutaneous T-cell lymphoma (CTCL). Early stages of the disease are characterized by eczema-like patches and often respond well to skin-directed treatments. However, approximately 25% of cases of early-stage MF may progress to a higher stage, characterized by recurrent infections and high mortality.1

In recent years, gene-sequencing-based approaches have greatly contributed to our understanding of the mutational landscape of CTCL, revealing the emergence of numerous subclones and complex patterns of clonal mutations.2 Alterations have been described in gene expression of key players of DNA damage (TP53, ATM), chromatin regulation (TOX, TWIST1), the Janus kinase/signal transducer and activator of transcription pathway (JAK3, STAT3, STAT4), T-cell receptor and cytokine signalling (CCR4, ZEB1), the nuclear factor-kB family (NFκB2, TNFRSF1B), phosphoinositide 3-kinase/protein kinase B signalling (CDKN2A, PTEN) and cell migration (PLS3, DNM3).2 Most of these studies were based on leukaemic CTCL, usually from Sézary syndrome (SS) due to its easy accessible tumour cells from peripheral blood.2–6 However, studies over the past decade have shown clearly that MF and SS are different diseases within the group of CTCL.1

In this issue of the BJD, Xiao et al.7 describe the mutational landscape of the lymphocytic infiltrate of MF by comparing early-stage plaques against late-stage plaques and tumours from the same patients. To focus on the specific genetic imprint of the MF tumour cells, they elegantly used laser-assisted skin microdissection. This permits a higher resolution of RNA expression of malignant lymphocytes, by excluding other components such as stromal cells from the analysis. The highly tumour-enriched RNA was then analysed by both whole-transcriptome and whole-exome sequencing. As a result, the authors confirm8 and describe novel upregulated signalling pathways in advanced MF lesions, for example meiomitosis, cell survival and proliferation, and DNA repair. Moreover, during progression they found overexpression of selected genes of pathways such as mitogen-activated protein kinase kinase/extracellular signal-regulated kinase, Akt and mammalian target of rapamycin, which decipher key elements of tumour progression in MF and beyond this are of potential therapeutical value. Furthermore, they found a high transcriptional similarity of malignant cells of tumoral lesions and late-stage plaques in MF. Based on the remarkable similarities of these different skin lesions at the level of the transcriptome, they interpret this as tumour cell percolation between these anatomically distant lesions via haematogenous self-seeding.

These results presented by Xiao et al. are significant because they highlight differences in the gene expression profile during the course of the disease. They also identify several candidate genes that broaden our understanding of tumour progression in CTCL. Furthermore, these findings may be exploited in further clinical trials with stratification of patients based on their specific genetic aberration, leading to personalized medicine.

Finally, a key finding of the authors is the high transcriptional similarity between the late-stage plaques and tumoral lesions, which is evidence of the common origin of these lesions. This leads to the hypothesis of percolation of the malignant cells and the clinical implication of the need for early eradication of emerging tumours, for example by radiotherapy. Although the precise mechanism of tumour percolation remains open, this hypothesis may be clinically supported by the work of O’Malley et al., who demonstrated that radiotherapy eradicates malignant T cells in MF, which is associated with improved survival in early-stage disease.9

In conclusion, the work of Xiao et al. broadens our understanding of tumour progression in MF and serves as a valuable basis for further investigations regarding the role of tumour percolation and its clinical impact.

Acknowledgments: Open Access funding enabled and organized by Projekt DEAL.

G. Dobos1 and C. Assaf1,2

1Department of Dermatology and Allergy, Skin Cancer Center Charité, Charité–Universitätsmedizin Berlin, Berlin, Germany; and 2Department of Dermatology and Venerology, HELIOS Klinikum Krefeld, Krefeld, Germany

Email: chalid.assaf@charite.de

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

References

1 Quaglino P, Fava P, Pilieri A et al. Phenotypical markers, molecular mutations, and immune microenvironment as targets for new treatments in patients with mycosis fungoides and/or Sézary syndrome. J Invest Dermatol 2021; 141:484–95.
2 García-Díaz N, Pitirí MÁ, Ortiz-Romero PL, Vaqué JP. Mycosis fungoides and Sézary syndrome: an integrative review of the
pathophysiology, molecular drivers, and targeted therapy. Cancers (Basel) 2021; 13:1931.
3 Tensen CP, Quint KD, Vermeer MH. Genetic and epigenetic insights into cutaneous T-cell lymphoma. Blood 2022; https://doi.org/10.1182/blood.2019004256.
4 Najidh S, Tensen CP, van der Sluijs-Gelling AJ et al. Improved Sézary cell detection and novel insights into immunophenotypic and molecular heterogeneity in Sézary syndrome. Blood 2022; https://doi.org/10.1182/blood.2021012286.
5 Gaydosik AM, Tabib T, Geskin LJ et al. Single-cell lymphocyte heterogeneity in advanced cutaneous T-cell lymphoma skin tumors. Clin Cancer Res 2019; 25:4443–54.
6 Steininger A, Möbs M, Ullmann R et al. Genomic loss of the putative tumor suppressor gene E2A in human lymphoma. J Exp Med 2011; 208:1585–93.
7 Xiao MZX, Hennessey D, Iyer A et al. Transcriptomic changes during stage progression of mycosis fungoides. Br J Dermatol 2022; 186:520–31.
8 Humme D, Haider A, Möbs M et al. Aurora kinase A is upregulated in cutaneous T-cell lymphoma and represents a potential therapeutic target. J Invest Dermatol 2015; 135:292–300.
9 O’Malley JT, de Masson A, Lowry EL et al. Radiotherapy eradicates malignant T cells and is associated with improved survival in early-stage mycosis fungoides. Clin Cancer Res 2020; 26:408–18.

Modulating mucins makes melanin

DOI: 10.1111/bjd.20877

The outermost layer of skin, the epidermis, has evolved to provide a physical barrier of protection from harmful substances and invasion of pathogens. The skin barrier consists in part of highly glycosylated proteins called mucins, and the epithelium. Epidermal homeostasis is maintained by the proliferation and differentiation of its basal layer keratinocytes that migrate to the superficial layer of the epidermis, and through its regulated intercellular communication with the pigment producing cells, the melanocytes. Together, they form a functional unit, the epidermal melanin unit, which maintains epidermis integrity and is responsible for skin pigmentation.1

The work developed by Kim and Choi2 aimed to correlate the expression levels of mucins with melanogenesis. For this, the authors found that Mucin-like protein 1 (MUCL1) has a negative correlation with pigmentation level and tyrosinase activity. MUCL1 was first identified as a breast-specific gene due to its most restricted mRNA expression, where it exerts an important role in breast cancer cell proliferation.3,4 Its limited expression in normal breast tissue makes MUCL1 an attractive tumour-associated antigen for targeted therapy of breast cancers. Significant mRNA expression levels of MUCL1 were previously reported in skin,4 but Kim and Choi further show that MUCL1 expression in melanocytes regulates the melanogenic pathway. They also clearly demonstrate that the effect of MUCL1 silencing in melanin biosynthesis can be rescued by the addition of the essential amino acid threonine, which constitutes a particularly interesting finding.

Melanin derives from the amino acid L-tyrosine, involving the action of at least three key melanogenic enzymes, tyrosinase and tyrosinase-related proteins-1 and -2;5, further, several amino acids, peptides and their analogues have been found to participate in fine-tuning pigmentation in the skin.6 Arising from the results presented by Kim and Choi,7 additional questions should now be addressed, to clarify if threonine inhibits tyrosinase activity directly or affects pigmentation by increasing MUCL1 levels. These studies can be used to develop new peptide-based drugs to control skin pigmentation disorders.

Additionally, mucins comprise a family of glycoproteins with diverse functions, establishing not only a mechanical barrier to pathogens, but also controlling proliferation and migration of epithelial cells.3,4 While mucins have been studied in other organs, their role in skin has received less attention. Importantly, mucin overexpression has been observed in several cutaneous malignancies,7 such as the rare primary mucinous carcinoma of the skin8 and in primary nonmetastatic melanomas.9 It will be of interest to study in more detail the expression of MUCL1 in melanoma cells, as Kim and Choi have established a first correlation between threonine supplementation to recover MUCL1 expression levels in a heavily pigmented melanoma cell line, derived from a metastasis. Melanomas are highly heterogeneous skin tumours resulting from the malignant transformation of melanocytes, and it has been observed that melanin presence in metastatic melanoma cells decreases the effect of radiotherapy.10 It will be of interest to further analyse the MUCL1 expression profile in melanomas and address the possible implications of MUCL1 regulation in the outcome of cutaneous skin tumour therapy.

To conclude, the studies developed by Kim and Choi reveal interesting observations for the pigmentation field, pointing to the need for future studies to explore the role of mucins in the control of melanin synthesis and distribution, with implications for a variety of skin conditions.

C. Casalou and D.J. Tobin

1The Charles Institute of Dermatology, School of Medicine, University College Dublin, D04 V1W8 Dublin, Ireland; and 2The Conway Institute of Biomolecular and Biomedical Research, University College Dublin, D04 V1W8 Dublin, Ireland

Email: cristina.casalou@ucd.ie

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

References
1 Weiner L, Fu W, Chirico WJ, Brissette J. Skin as a living coloring book: how epithelial cells create patterns of pigmentation. Pigment Cell Melanoma Res 2014; 27:1014–31.
2 Kim J, Choi H. The mucin protein MUCL1 regulates melanogenesis and melanoma genes in a manner dependent on threonine content. Br J Dermatol 2022; 186:532–43.