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Machine Learning-Driven Integration of SERS for the Minimally Invasive Diagnosis of Keratinocyte Carcinomas

Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) are the two most common keratinocyte carcinomas, accounting for over 95% of non-melanoma skin cancers worldwide and representing a substantial healthcare burden [1]. Although histopathology remains the diagnostic gold standard, a definitive diagnosis requires an invasive biopsy, highlighting the need for rapid, minimally invasive diagnostic approaches. This study investigated the application of surface-enhanced Raman spectroscopy (SERS) of blood plasma using gold-coated silicon nanopillar SERSTRATE® (Silmece) substrates in combination with the SKiNET machine learning framework [2]. Plasma samples from ten individuals in each cohort (BCC and healthy controls (HC)) and nine individuals with SCC were analyzed using SERS. Spectral datasets were interrogated using partial least squares discriminant analysis (PLS-DA), receiver operating characteristic (ROC) analysis and SKiNET support vector machine (SVM) classification. Binary SVM classification achieved average sensitivities/specificities of 81.94%/84.24%, 93.57%/92.18% and 92.57%/94.61% for BCC vs HC, SCC vs HC and SCC vs BCC, respectively. ROC analysis demonstrated excellent discriminatory performance, with AUC values of 0.831 [95% CI 0.765–0.897] for BCC vs HC, AUC=0.9298 [95% CI 0.892–0.966] for SCC vs HC, and AUC=0.936 [95% CI 0.912–0.960] for SCC vs BCC. The PLS-DA model identified discriminatory biochemical features between disease groups. BCC versus HC demonstrated significant Raman shifts at 1186 cm⁻¹ (*p < 0.05), corresponding to amino acid and carbohydrate-related vibrations, and 1640 cm⁻¹ (*p < 0.05), corresponding to the amide I band associated with protein secondary structure. SCC versus HC exhibited significant Raman shifts at 1650 cm⁻¹ (*p < 0.05), corresponding to the amide I band of proteins and C=C stretching of unsaturated lipids, and 1776 cm⁻¹ (*p < 0.05), corresponding to carbonyl (C=O) stretching of lipids and ester groups [3]. Collectively, these spectral alterations indicate disease-associated changes in protein conformation, lipid composition and metabolic profile. These findings demonstrate that SERS combined with the SKiNET machine learning framework can accurately discriminate keratinocyte carcinoma subtypes from healthy controls while identifying biologically relevant spectral biomarkers. This approach shows promise as a rapid, minimally invasive adjunct for the diagnosis and classification of keratinocyte carcinomas.

References

- [1] Venables ZC, Nijsten T, Wong KF, Autier P, Broggio J, Deas A, Harwood CA, Huws DW, Langan SM, Morgan E, Mitchell H, Proby CM, Rashbass J, Leigh IM, British Journal of Dermatology, 181(3) (2019) 474–482
- [2] Banbury, C., Mason, R., Styles, I., Eisenstein, N., Clancy, M., Belli, A., Logan, A., & Oppenheimer, P. G., *Scientific Reports*, 9 (2019) 10812
- [3] Z. Movasaghi, S. Rehman, and I. U. Rehman, *Applied Spectroscopy Reviews*, 42(5) (2007) 493–541