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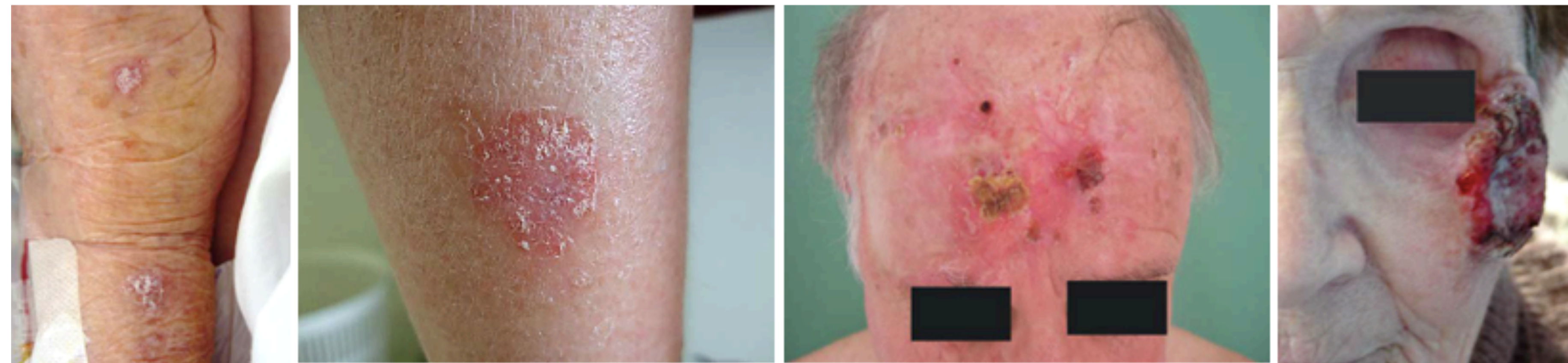
No conflicts of interest

## Introduction

Exposure to ultraviolet (UV) radiation from the sun is the most significant risk factor resulting in non-melanoma skin cancers (NMSCs), including cutaneous squamous cell carcinomas (cSCCs) which their incidence rates are still on the rise.

cSCCs typically manifests as a spectrum of progressively advanced malignancies, ranging from a precursor actinic keratosis (AK) to squamous cell carcinoma (SCC), **in situ**, **invasive** cSCC and finally **metastatic**<sup>1</sup>.

A better understanding of molecular changes involved in the transformation of this UVB-induced precancerous lesions (actinic keratosis (AK)) to localized tumors and then metastasis will aid in early detection, development of biomarkers and future targeted strategies<sup>2,3</sup>.



Actinic Keratosis (AK)

In situ cSCCs

Invasive cSCCs

Metastasis

Skin carcinogenesis in multiple stages

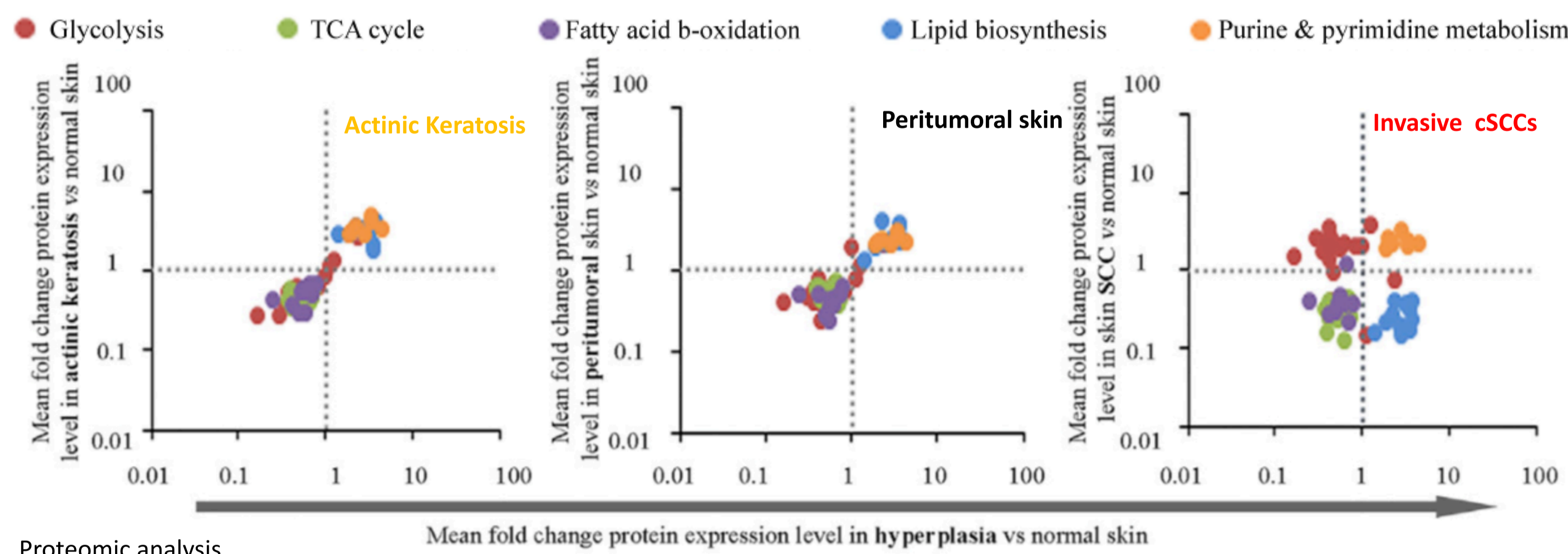


## Research Highlights

- Characterize the molecular and metabolic features of cSCCs at different stages of carcinogenesis
- Identify the immunologic landscape of cSCCs at different stages of carcinogenesis
- Uncover relevant biomarkers predicting the cSCCs evolution risk.

## Results

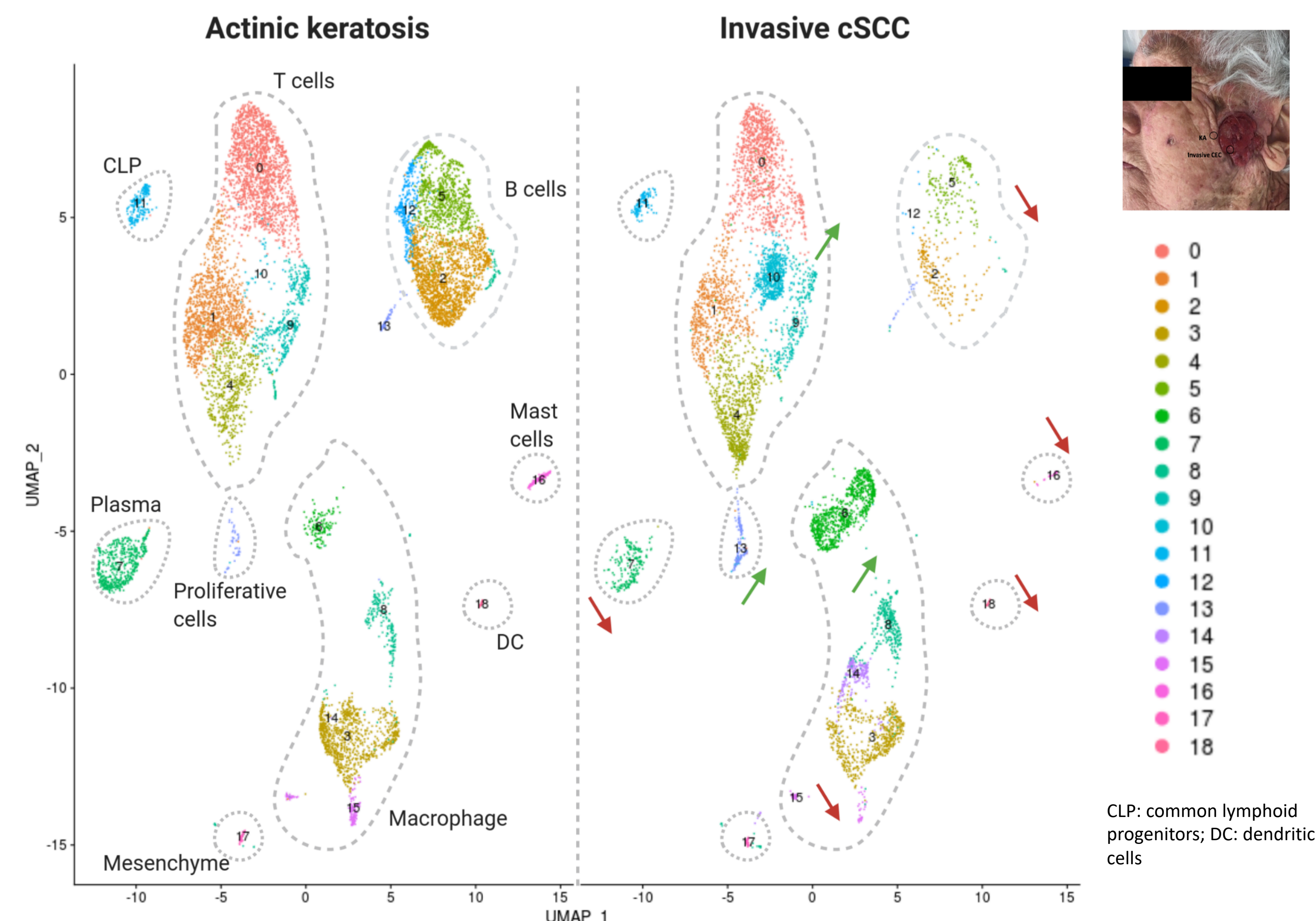
- 1-Very similar metabolic pathways are involved in hyperplasic, AK and peritumoral tissue
- 2-On the contrary, metabolic profile of tumors are differing from precancerous lesions



Proteomic analysis

- Downregulation in lipid biosynthesis and upregulation in glycolysis
- Persistent Purine and Pyrimidine metabolic pathway
- Specific metabolic modifications, of which some persists throughout tumor development, occur at a very early stage of skin carcinogenesis

## 3- Several immune cell subset are depleted in cSCC compared to AK or enriched

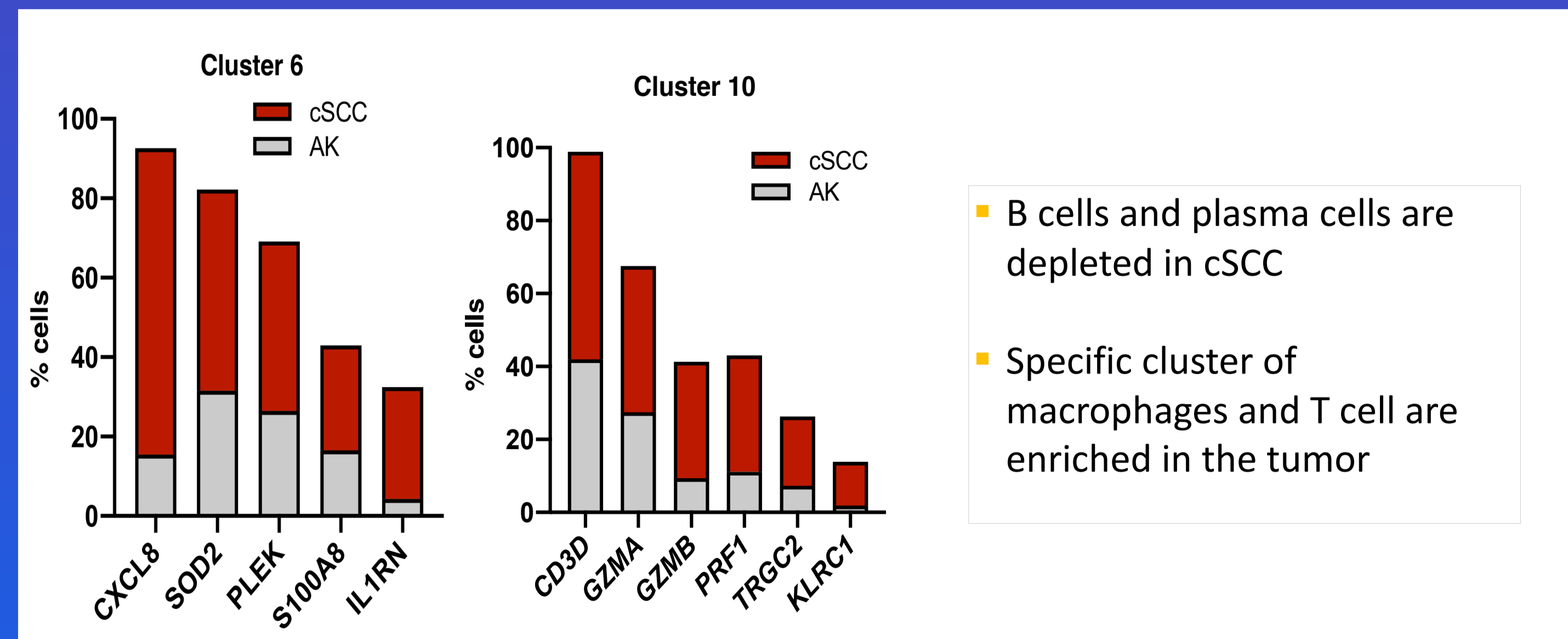


CLP: common lymphoid progenitors; DC: dendritic cells

## 4-Inter-patient metabolic heterogeneity



- Metabolic profiles differ in subgroups of patients including OXPHOS and glycolysis



- B cells and plasma cells are depleted in cSCC
- Specific cluster of macrophages and T cell are enriched in the tumor

## Conclusion

- ✓ Improving diagnostic accuracy of skin precancerous lesion could be of help to reduce current strong economic burden of AK clinical management.
- ✓ Our data suggest that metabolic and immune features of cSCC could be used as pertinent biomarkers for stratification of cSCC and predicting their evolution risk.

<sup>1</sup> Ratushny V et al. From keratinocyte to cancer: the pathogenesis and modeling of cutaneous squamous cell carcinoma. J Clin Invest. 2012;122(2):464-72.  
<sup>2</sup> Hosseini M, Dousset L, et al. Energy Metabolism Rewiring Precedes UVB-Induced Primary Skin Tumor Formation. Cell Rep. 2018. 23(12):3621-3634  
<sup>3</sup> Hosseini M, Dousset L, et al. UVB-induced DHODH upregulation, which is driven by STAT3, is a promising target for chemoprevention and combination therapy of photocarcinogenesis. Oncogenesis 2019.