574 The association of Hypoxia-Inducible Factor α (HIF1α) and epithelial-menchymal transition (EMT)-related markers in basal cell carcinoma.

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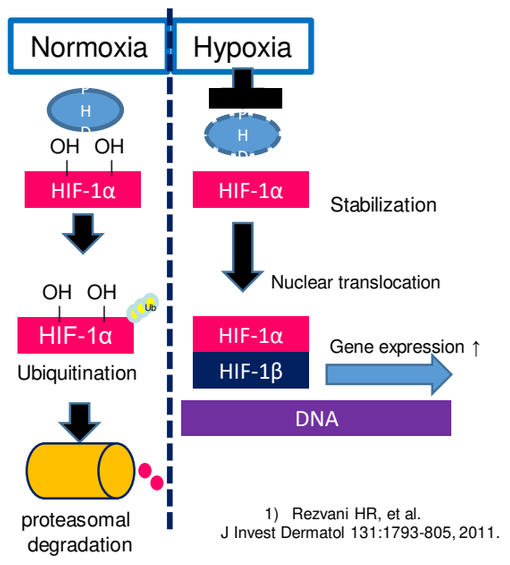
Background

- **HIFs are・・・**
  - basic helix-loop-helix transcription factor regulated by hypoxia [1].
  - heterodimeric proteins composed of two subunits, HIF1α and HIF-1β.

HIF1α is・・・
- expressed in several hypoxic tissues including epidermis.
- associated with angiogenesis, ECM remodeling, cell proliferation, and epithelial mesenchymal transition (EMT).



1) Rezvani HR, et al. J Invest Dermatol 131:1793-805, 2011.

HIF1α in skin cancer

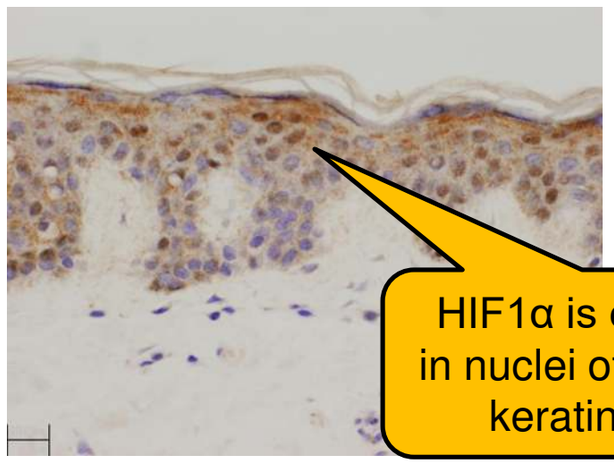
- **Malignant melanoma and Squamous cell carcinoma(SCC) [2)~5)]**
  - HIF-1α expression is associated with tumor invasion and poor prognosis.

2) Kumar SM, et al. Cancer Res 67:3177–84, 2007.
3) Spinella F, et al. Cancer Res 67:1725–34, 2007.
4) An X, et al. J Dermatol 41:76-83, 2014.
5) Mendes SO, et al. PLoS One 9:e84923, 2014.

Objective

- To elucidate the association of HIF1α and EMT-related markers in basal cell carcinoma.

HIF1α expression in normal epidermis



Material and methods

- Specimen
  - Formalin-fixed and paraffin-embedded tissue sections were obtained from 12 patients with each BCC subtype (total 24 patients).

BCC subtypes	Nudular	Morphea
Average age (year)	82.6	69.6
Male : Female	4:8	2:10

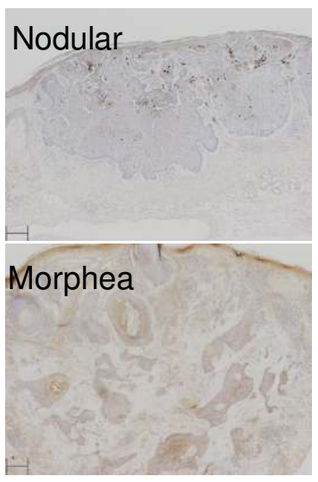
*** IHC Scoring (HIF1α, αSMA, Twist, Snail, N-cad)**
Score 0 0% , Score 1 <10% , Score 2 10~30% , Score 3 >30%

*** IHC Scoring (E-cad)**
Score 0 (not detected), 1 (lower), 2 (equal to), or 3 (higher) than normal epidermis

- Antibody
- Rabbit polyclonal anti-HIF1α: Novubio
- Mouse monoclonal anti-αSMA : DAKO
- Rabbit polyclonal anti-Twist: abcam
- Gout polyclonal anti-snail: abcam
- Mouse monoclonal anti-E-cadherin : BD
- Rabbit polyclonal anti-N-cadherin : BD

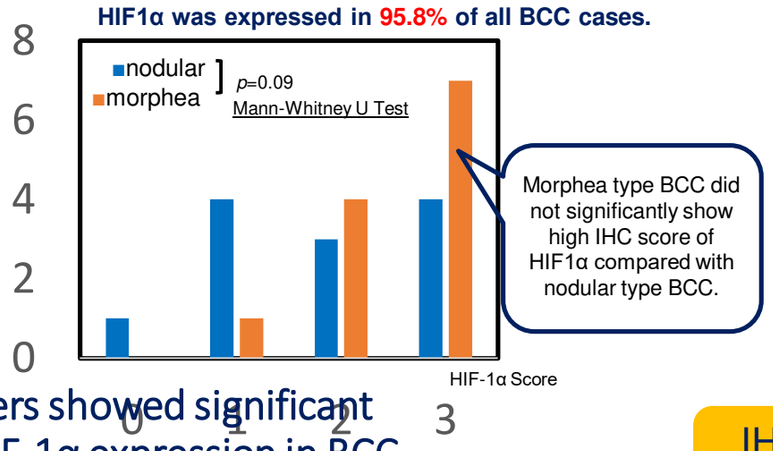
Resutls

The expression of HIF1α in BCC



IHC Score	0	1	2	3
Hif-1α	1 (4.2%)	5 (20.8%)	7 (29.2%)	11 (45.8%)

HIF1α was expressed in 95.8% of all BCC cases.



Several EMT markers showed significant correlation with HIF-1α expression in BCC

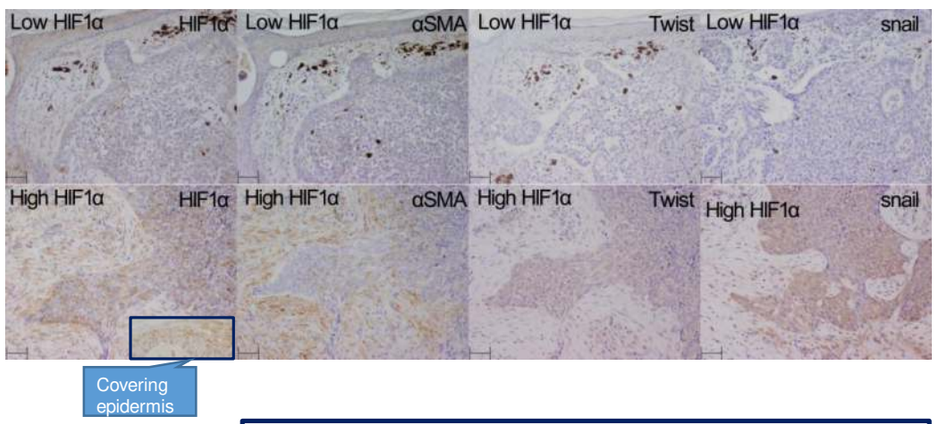
HIF1α vs. EMT markers (IHC score)

<positive correlation>
Spearman's correlation coefficient by rank test

EMT markers	rs	*p* value
αSMA	0.714	0.001
Snail	0.568	0.008
Twist	0.802	0.0002
N-cadherin	0.439	0.51

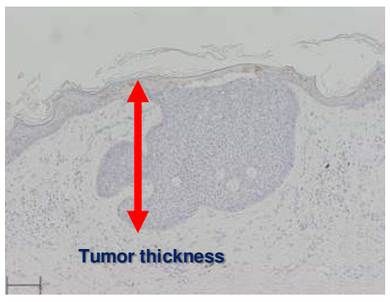
<negative correlation>

E-cadherin	-0.06	0.116



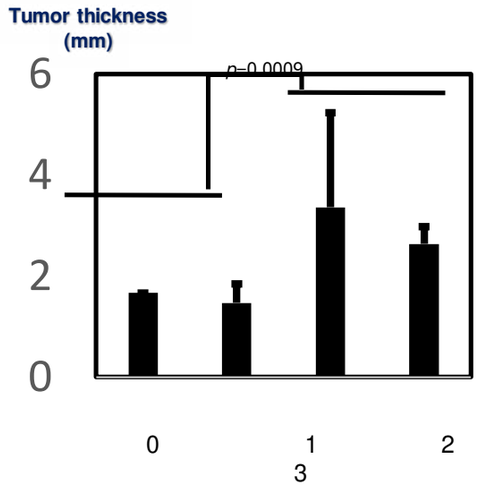
Snail, Twist and αSMA showed significant correlation with HIF1α expression in BCC.

High HIF1α expression was associated with tumor thickness in nodular BCC.



Tumor thickness [6)]: The maximal tumor invasion was measured from top of the granular layer to the deepest point of penetration.

6) Abreo F, *et al.* J Am Acad Dermatol. 25:1005-11, 1991.



High HIF1α and αSMA expression had significant correlation with tumor thickness in nodular BCC.

IHC score vs Tumor thickness (mm) in each BCC subtype

Spearman's correlation coefficient by rank test

<HIF1α>

BCC subtypes	rs	*p* value
Nodular	0.709	0.02
Morphea	0.24	0.638

<αSMA>

Nodular	0.751	0.013
Morphea	0.052	0.834

<Twist>

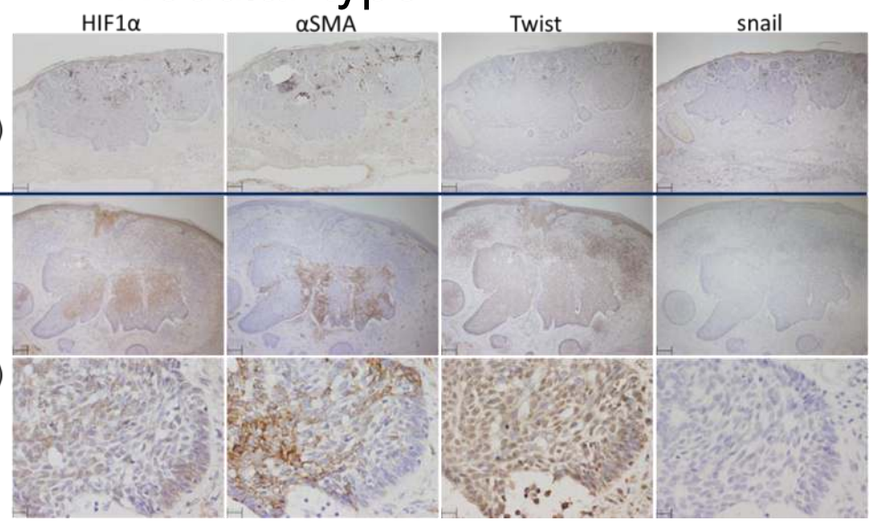
Nodular	0.519	0.09
Morphea	0.220	0.781

<Snail>

Nodular	-0.147	0.503
Morphea	-0.267	0.159

High HIF1α, αSMA and Twist expression were shown in thick nodular BCC.

Nodular type



Summary

- HIF1α was expressed in 95.8% of all BCC cases.
- Several EMT markers such as αSMA and Twist showed significant correlation with HIF-1α expression in BCC.
- High HIF1α and related EMT marker's expression was associated with tumor thickness in nodular BCC.

Conclusion

- HIF1α expression may be associated with αSMA and Twist expression in BCC.
- HIF1α expression may be associated with tumor invasion through αSMA expression in nodular type BCC.