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| 原文題目(出處)： | **Cell genomics and immunosuppressive biomarker expression influence PD-L1 immunotherapy treatment responses in HNSCC-a computational study** |
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內文：

1. **study objectives:**

   Demonstrating a need for a more accurate method to identify those who will respond before immunotherapy.

   PD-1&PD-L1: Overexpression of PD-L1 on tumor cells skews anti-tumor immunity by impeding anti-tumor CD8+ T-cell function through inhibition of T-cell proliferation, reduction of T-cell survival, inhibition of cytokine release, and promotion of T-cell apoptosis.

   所以若可阻斷 PD-1 或是 PD-L1 即可使 T-cell 有功能(目前大多數藥物都是抑制 PD-1，如: Nivolumab，Pembrolizumab；抑制 PD-L1 的臨床藥物有 Atezolizumab 和 Avelumab)

   目前這兩種免疫藥物的 objective response rate 最高只有 24.8%

**Table I.** Objective response rates in HNSCC trials assessing antibodies against PD-1 and PD-L1

| *Checkpoint inhibitor study (Reference)* | *Objective response "responder rate" (No. of patients)* | *Calculated "nonresponder rate"* |
|---|---|---|
| PD-1 | | |
| Pembrolizumab (MK-3475)[9,49] | 19.6% (56) | 80.4% |
| Pembrolizumab (MK-3475)[50] | 24.8% (150) | 75.2% |
| Nivolumab (BMS-936558)[9,17,50] | Study is ongoing | |
| Pidilizumab (CT-011)[9,17] | Study is ongoing | |
| PD-L1 | | |
| MPDL3280 A[51] | 20.5% (122) | 79.5% |
| MEDI4736[52] | 14.0% (22) | 86.0% |
| Durvalumab (MEDI4736)[50,53] | 12.0% (62) | 88.0% |

*HNSCC*, head and neck squamous cell carcinoma; *PD-1*, programmed death 1; *PD-L1*, programmed death–ligand 1.

2. **Study design:**

   A. identified deleterious gene mutations in **SCC4, SCC15, and SCC25** and created cell line

   B. **24 immunosuppressive biomarkers** were predicted and used to sort cell lines into those that would respond to PD-L1 immunotherapy and those that would not.

   C. We hypothesized that HNSCC tumor cell genomics influences cell signaling and downstream effects on the expression of PD-L1, chemokines, and immunosuppressive

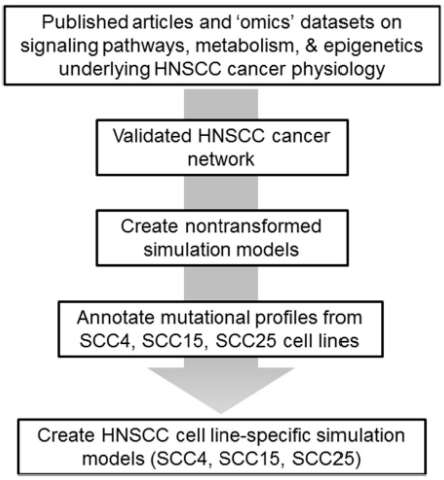
biomarkers and that these profiles can be used to **predict clinical responses in patients.**

## 3. Materials and methods

### A. Sitmulation model

i. Cell line:SCC4,SCC15,SCC25→exam exomes from each cell line for deleterious gene mutations

ii. Simulation models:create predictive computational simulation models




iii. The models **did not contain cell line** - specific deleterious gene mutation profiles and were simulated to reach a homeostatic steady state, which served as the control **baseline** for the biomarkers of interest.

iv. Specific **deleterious gene mutation profiles were converted into a computational format** and annotated into the HNSCC cancer network, simulated to induce the cell line - specific cancer disease states, and used to **predict the expression of 24 chemokines and immunosuppressive biomarkers**.

### B. Immunosuppressive biomarkers

i. 9 chemokines can trafficking dendritic cells into tumor microenviroment

ii. 14 biomarkers act as immunosuppressive mediatiors

iii. Calculate the index with **([D - C]/C)*100**, where C is the absolute value of the nontumorigenic baseline control (mM), and D is the absolute value of the biomarker obtained in the cell lineespecific cancer state network(mM)

**Table II.** The predicted expression of chemokines compiled into a DC infiltration index

| *Chemokine* | *SCC4 (%)* | *SCC15 (%)* | *SCC25 (%)* |
|---|---|---|---|
| CCL11 | −3.61 | 5.84 | 3.61 |
| CCL20 | −0.26 | 7.06 | 4.73 |
| CCL2 | −10.22 | 18.12 | 7.62 |
| CCL3 | −2.10 | 2.54 | 0.65 |
| CCL4 | 21.53 | 25.58 | 4.44 |
| CCL5 | −2.91 | 3.53 | 1.95 |
| CCL7 | −3.69 | 6.73 | 4.08 |
| CX3 CL1 | −0.79 | 5.57 | 3.45 |
| CXCL14 | −0.89 | −0.83 | −1.16 |
| **DC infiltration index** | **−2.95** | **74.14** | **29.37** |

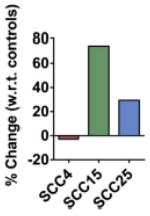
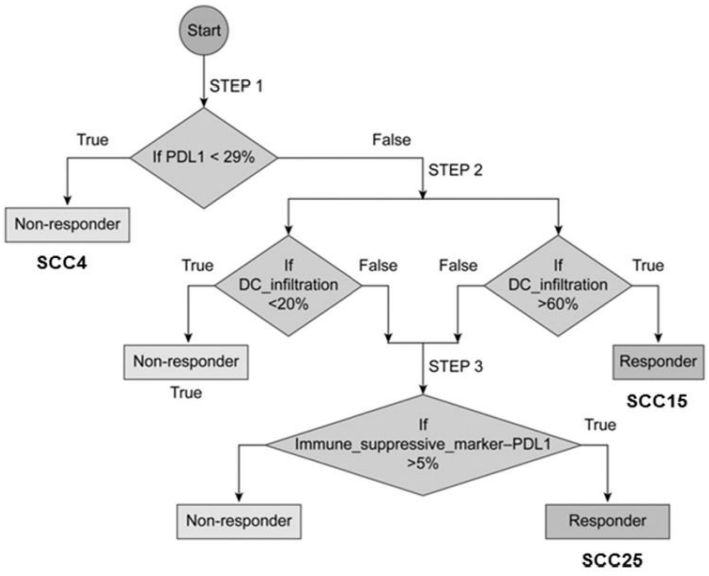



**Table III.** The predicted expression of PD-L1, dendritic cell infiltration index, and immunosuppressive biomarkers from simulation models of SCC4, SCC15, and SCC25

| *Markers and index* | *SCC4 (%)* | *SCC15 (%)* | *SCC25 (%)* |
|---|---|---|---|
| PD-L1* | 11.14 | 49.29 | 91.38 |
| Dendritic cell infiltration index | −2.93 | 74.11 | 29.38 |
| Immunosuppressive biomarkers | | | |
| TGF-β1 | 5.66 | 58.8 | 24.38 |
| IDO1 | 17.29 | 2.75 | 4.97 |
| IL-6 | −8.49 | 406.78 | 42.45 |
| VEGFA | 44.18 | 78.23 | 26.78 |
| TDO2 | 2.74 | 2.39 | 18.29 |
| $PGE_2$ | 39.04 | 39.19 | 26.97 |
| IL-10 | 2.01 | 46.53 | 26.09 |
| LGALS9 | −49.72 | 5.15 | 10.82 |
| FASLG | −1.05 | −2.98 | −4.96 |
| CD47 | 5.36 | 14.39 | 8.21 |
| CTLA-4 | 27.89 | 80.37 | 10.38 |
| PDCD1 LG2 | 3.6 | 7.89 | 5.65 |
| Ganglioside GM3 | −4.39 | 48.69 | 36.44 |
| Ganglioside GD2 | −4.39 | 48.69 | 36.44 |

### C. Predicted response to PD-L1 immunotherapy

i. Use calculated index to sort cell lines into those that would respond to PD-L1 immunotherapy and those that would not




4. Results

### A. Predictions of biomarkers

different items have different affect on each cell lines

### B. Predicted response to PD-L1 immunotherapy

SCC4 had 11.14% predicted PD-L1 expression →immunotherapy nonresponder

SCC15 had 49.29% predicted PD-L1 expression →immunotherapy responder

SCC25 had 91.38% predicted PD-L1 expression →immunotherapy responder

### C. Predicted pathway comparisons

Genes on cell lines that influence immunosuppressive biomarker expression

SCC4:TP53, CDK6, CCND1, NF1
SCC15 :EGFR, PIK3 CB, DUSP22, MAP3 K1
SCC25:TP53, CDKN2 A, LAMTOR5.

**5. Discussion**

A. This study determined the expression levels of 24 chemokines and immunosuppressive biomarkers.

**B. SCC15 and SCC25, cell lines originally from patients with HNSCC, would likely respond to PD-L1 immunotherapy treatment.**

**C. SCC4, a cell line from a patient with HNSCC, would not likely respond to PD-L1 immunotherapy treatment**

D. Why choose PD-L1?
It is expressed in **46%-100%** of human HNSCC biopsy specimens across multiple primary sites

E. These three step cut-offs has been used to predict PD-1 responder on small cell lung cancer therapy.

**6. Conclusion**

These models will be able to complement IHC results or provide effective where IHC is unfeasible, identify factors that influence PD-L1 expression, and **serve as a clinical decision support system to classify patients into those that would respond to PD-L1 immunotherapy and those that would not base on patient's deleterious gene mutation profile**.

| 題號 | 題目 |
|---|---|
| 1 | Which is true below about head and neck SCC ?<br>(A) Usually, it can be detected at early stage<br>(B) HNSCC has no connection with factors such as gender,age,race<br>(C) Treatment of HNSCC includes surgery,radio therapy,chemotherapy,gene therapy and immunotherapy<br>(D) Distant metastasis is common in HNSCC and usually affects the choice of therapy |
| 答案<br>(C ) | 出處： Burket's Oral Medicine 11th edition,Chapter 7 |
| 題號 | 題目 |
| 2 | Which description below about PD-1 and PD-L1 is wrong ?<br>(A) Overexpression of PD-L1 on tumor cell decrease T-cell function<br>(B) We have develop sufficient method to identify patients who are adequate to immunotherapy of HNSCC<br>(C) Nivolumab and Pembrolizumab inhibits PD-1 function<br>(D) PD-L1 express in most of HNSCC biopsy specimens |
| 答案<br>(B ) | 參考本篇研究<br>目前臨床上投藥有效的比率最高為 24.8%( Pembrolizumab)並不高 |