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Gaylord National Hotel
& Convention Center



Society for Immunotherapy of Cancer

SITC
2017

Dysfunction of dendritic cells in lung cancer

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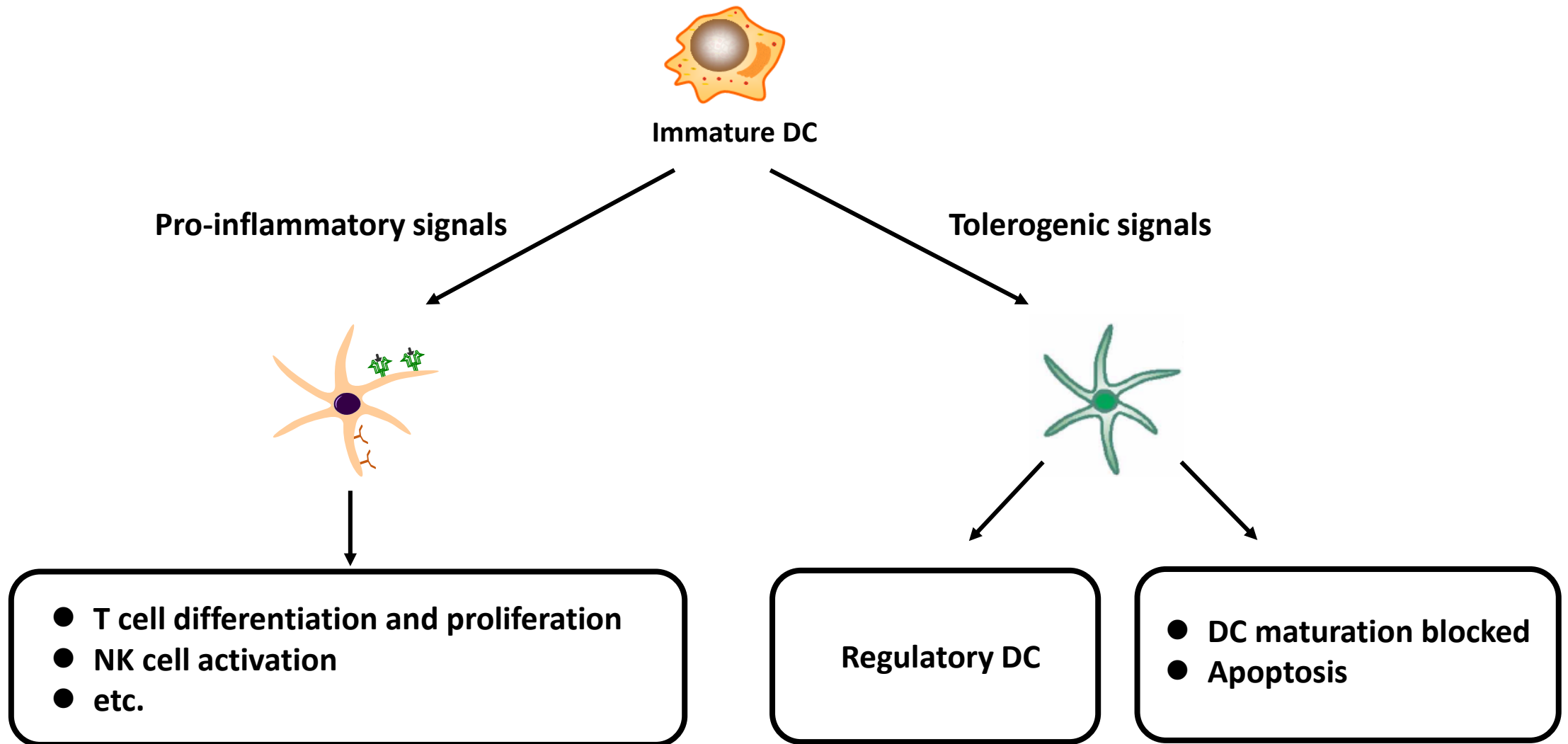
Society for Immunotherapy of Cancer

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Presenter Disclosure Information

<Fang Fang>

No Relationships to Disclose.



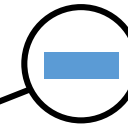
Tumor environment

Tumor-derived DC **activators**

- Tumor-associated antigens
- Heat-shock proteins
- High-mobility group box 1
- Pro-inflammatory signals
- Etc.

Tumor-derived DC **inhibitors**

- Anti-inflammatory signals
TGF- β , VEGF, IL-10, etc.
- Microvesicles
- Lactic acid
- Etc.



Immature DC

- What is molecular mechanism of DC integrated signals from activators and inhibitors?
- Which model better represent tumor environment?

Current models of tumor-induced DC dysfunction

In Vitro model

- **Tumor cell line conditioned medium associated DC**

Journal of Biological Chemistry 2012, Journal of Immunology 2011, etc..

**Simple complexity
of tumor environment**

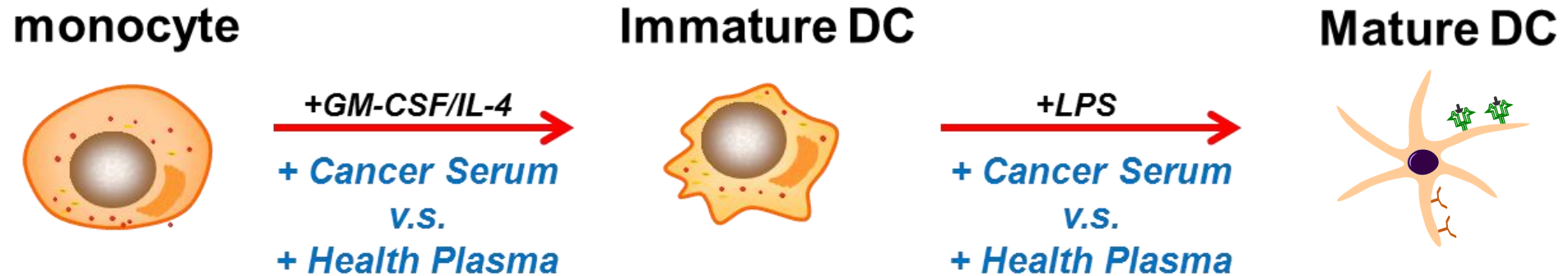
In Vivo model

- **Tumor-Infiltrating DC (TIDC)**

Blood 2014, Nature Immunology 2012, Medical Oncology 2011, Cancer Research 2007, etc..

Low abundance

A new in vitro model of tumor-induced DC dysfunction



Tumor environment: Cancer patients' sera

- Well-represented tumor environment.
- Health donator sample as control.

Criteria for clinical samples

- Tumor serums from patients in late stage of NSCLC, were sampled before treatment.
- Health plasma were collected from random health donor.
- Pool of multiple samples.

NSCLC patients serum

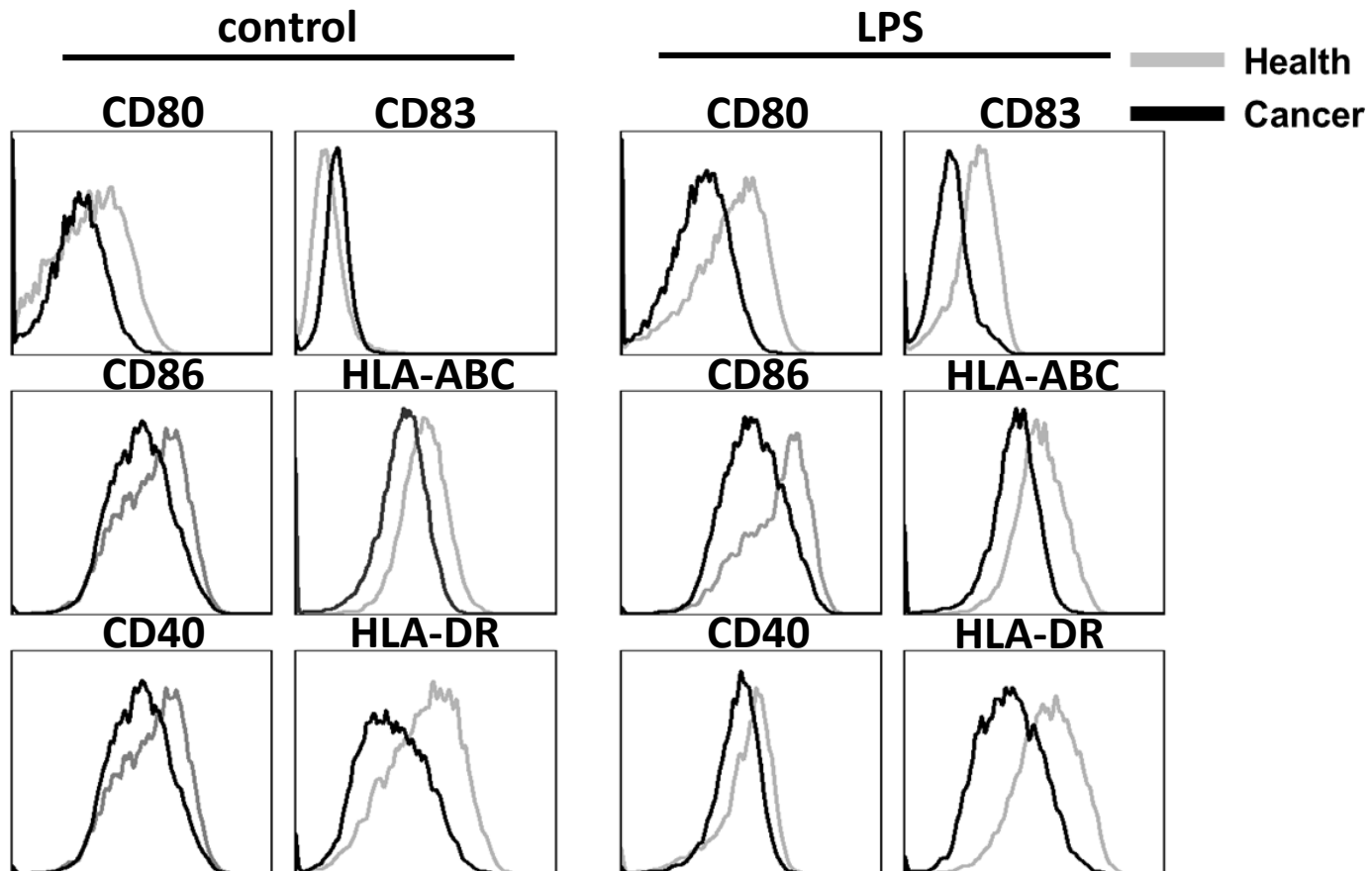
- Male 41, Female 15
- Age 44-76
- Blood type: A / B / O / AB
- Time: 2008.07 – 2009.02

Health plasma

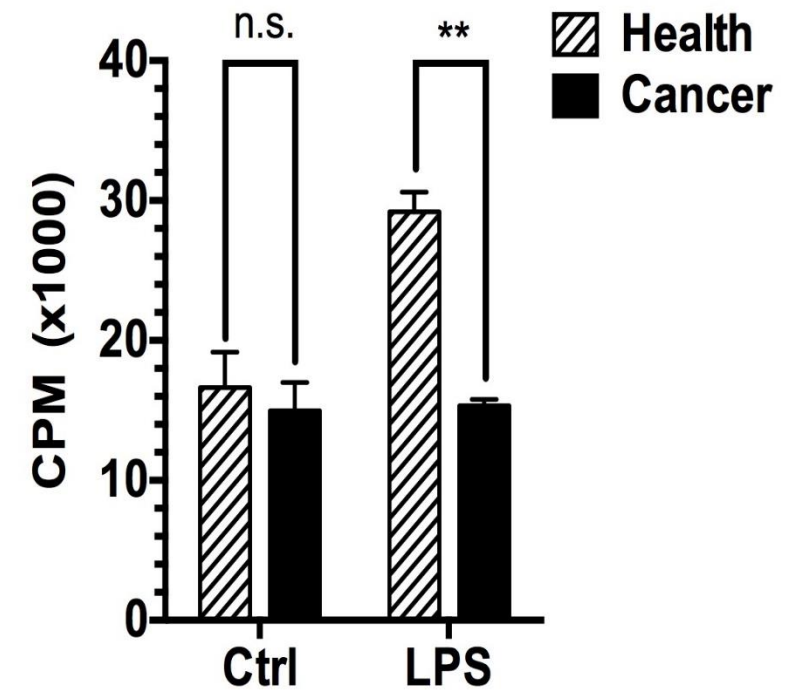
- Male 6, Female 2
- Age 24-45
- Blood type: A / B / O / AB
- Time: 2008.07 – 2009.02

Tumor-induced DC deficiency in vitro (1)

Cell surface molecules

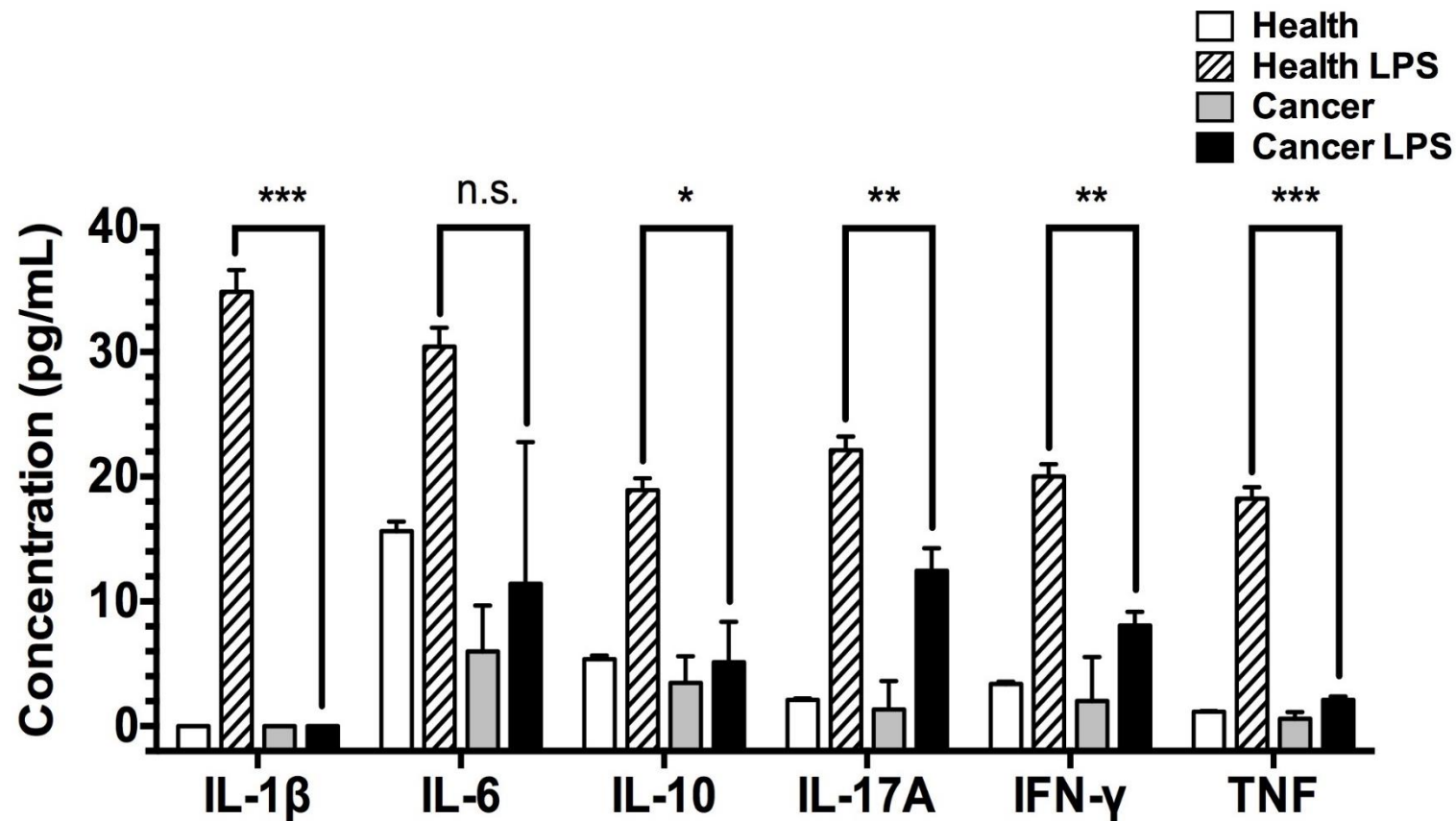


Antigen presenting

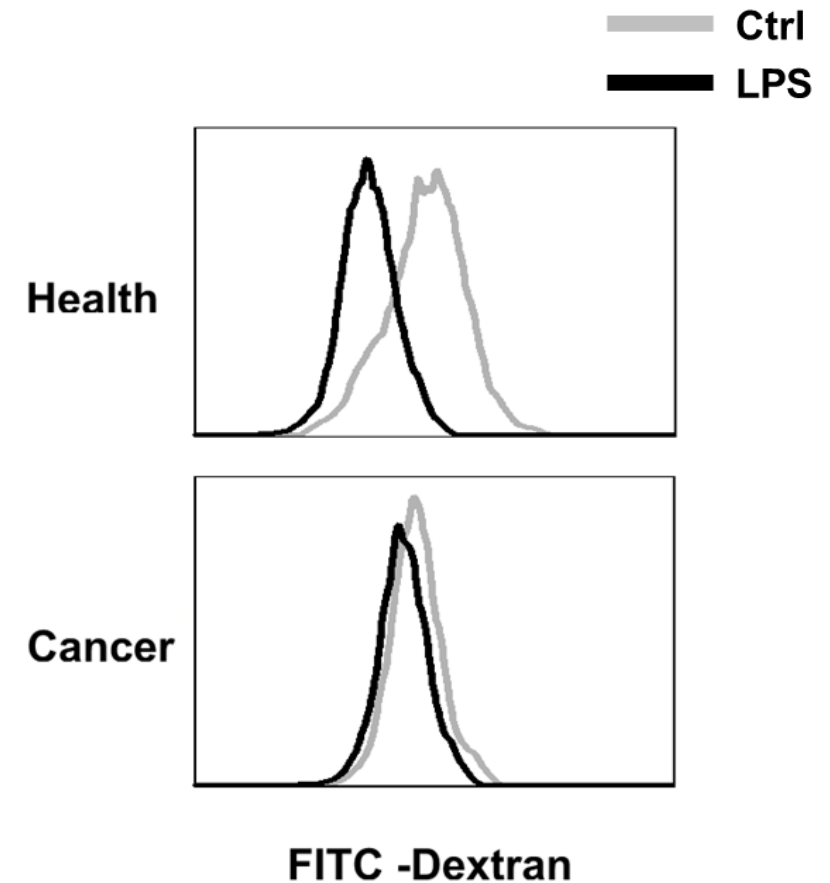


Tumor-induced DC deficiency in vitro (2)

Cytokine production



Endocytic activity



monocyte



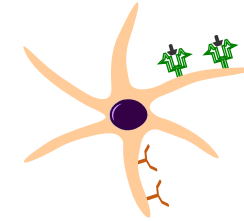
+GM-CSF/IL-4
+ tumor serum

Immature DC



+LPS
+ tumor serum

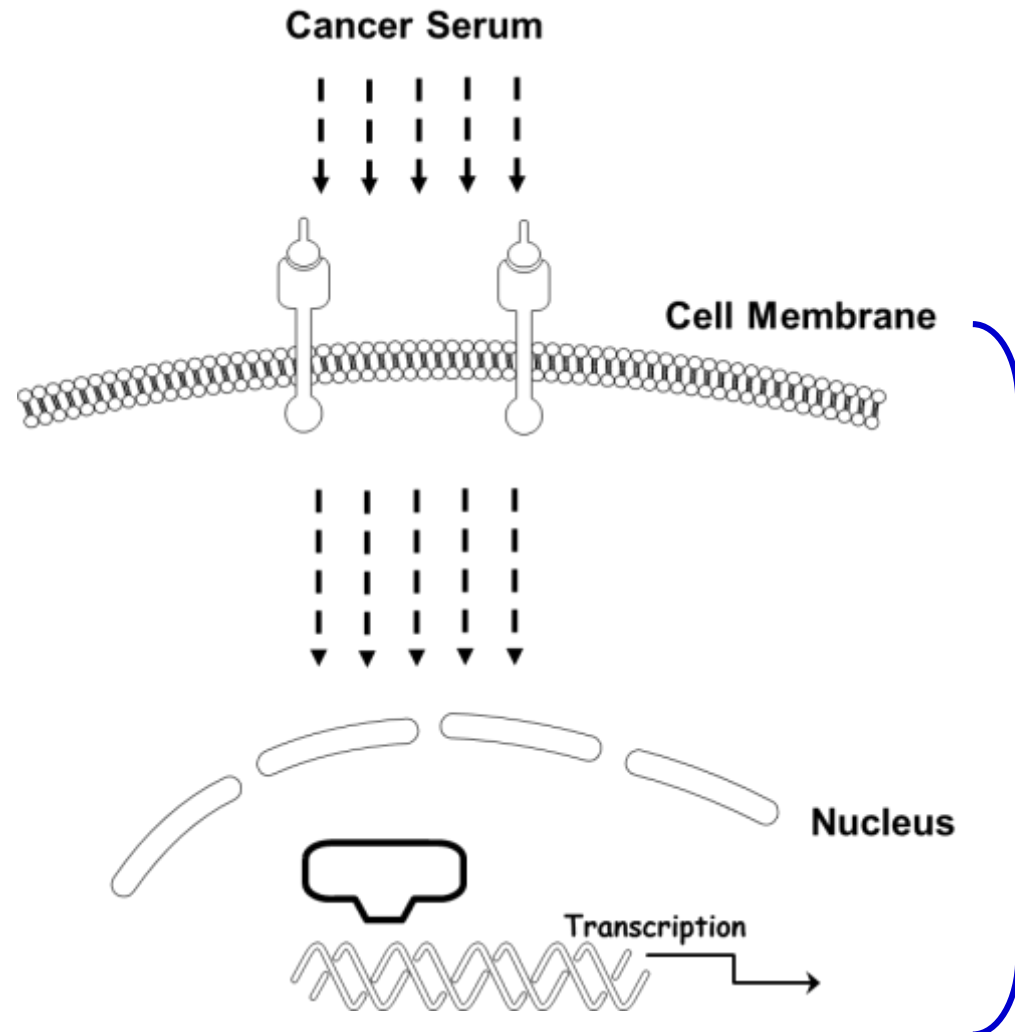
Mature DC



- ✓ Reduced co-stimulatory molecules
- ✓ Reduced cytokine production
- ✓ Suppressed endocytic activity
- ✓ Inhibited antigen-presenting

consistent with previous reports

- ✓ Do not induce cell apoptosis.
- ✓ Altered CAM expression.

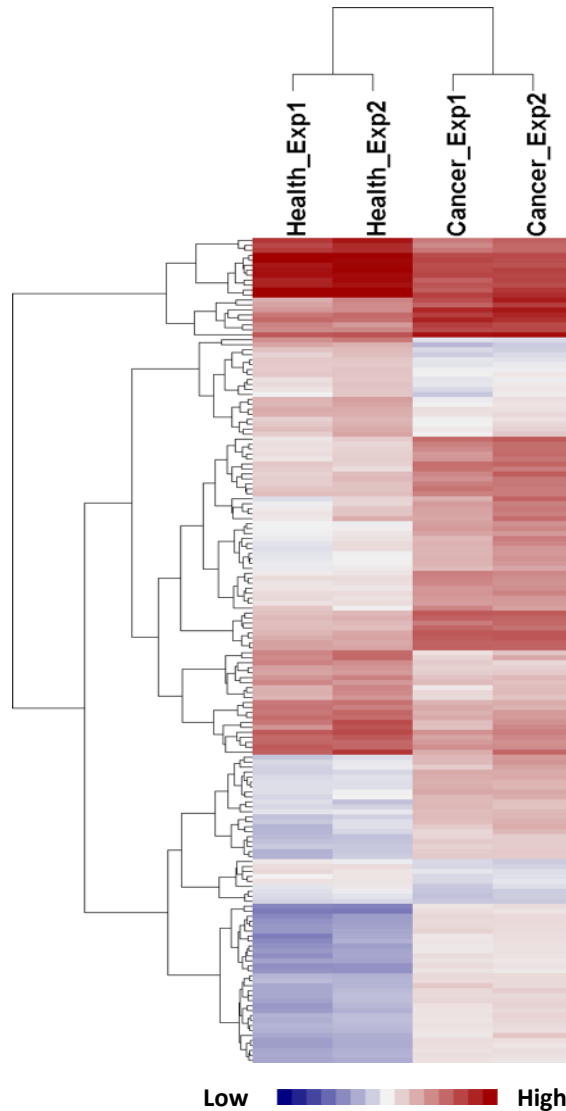


Mechanism of tumor-induced DC dysfunction.

- Transmembrane receptor
- Transcription factor
- Expression profile

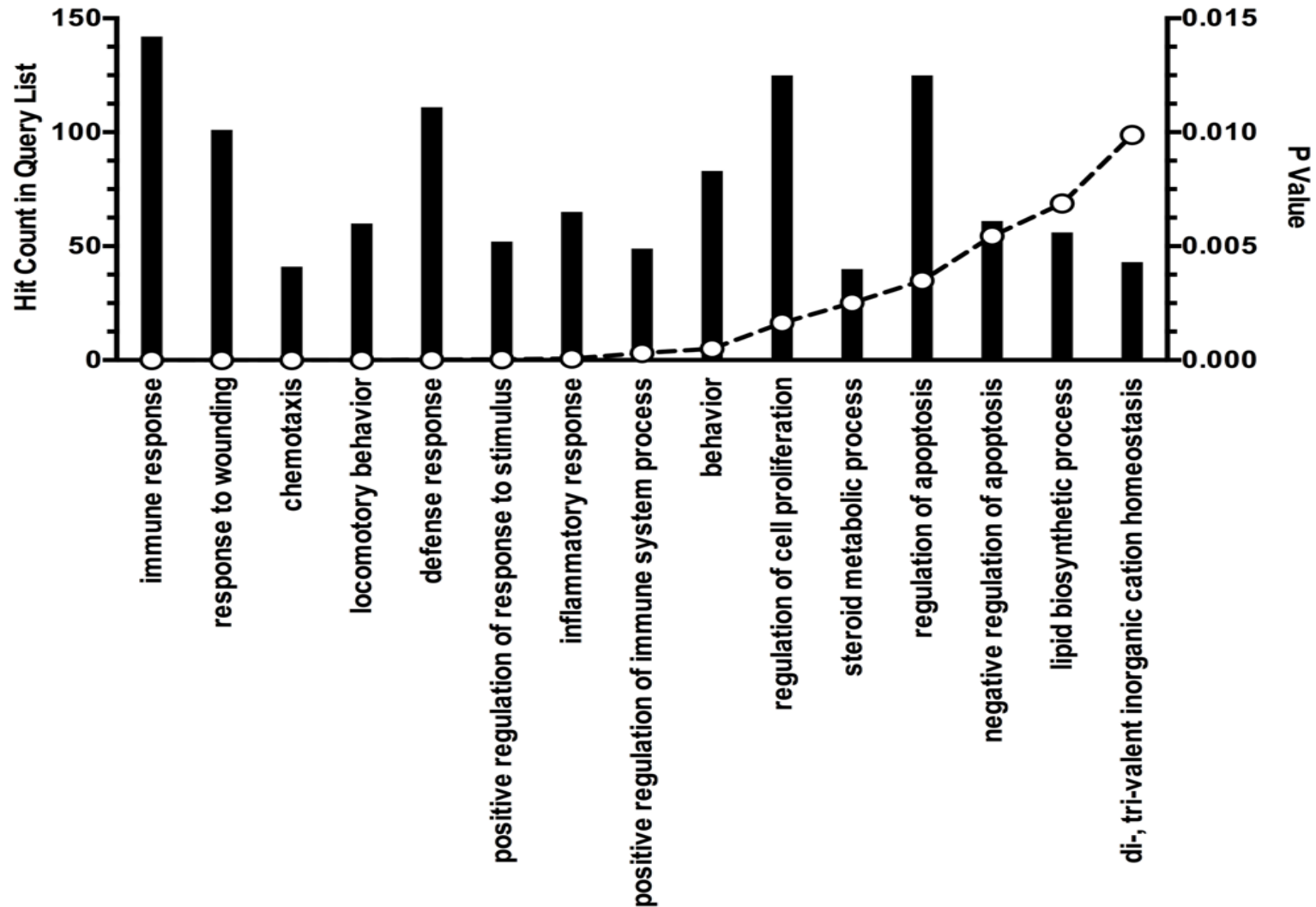
Gene expression profiling in cancer-induced iDC

A

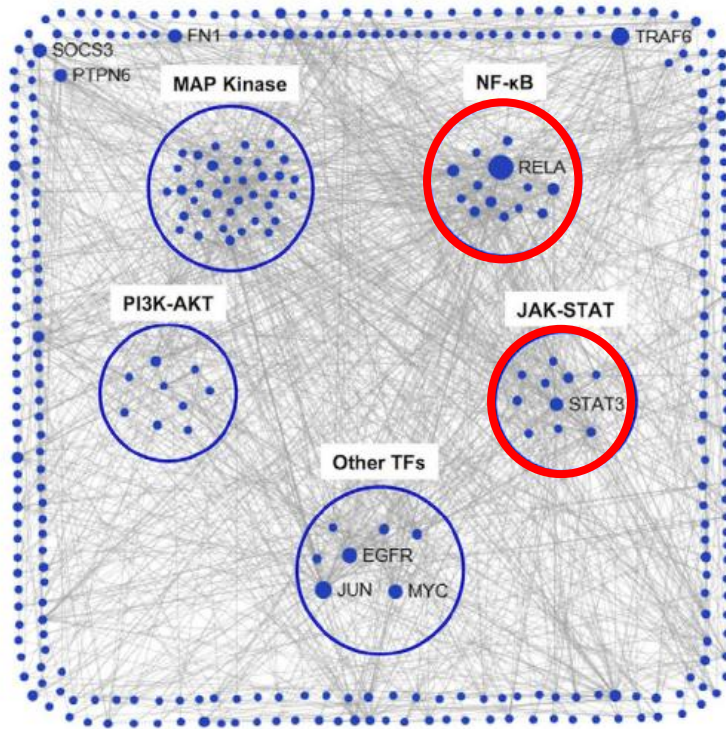


- Operon Human Genome Array-Ready Oligo Set
- 22484 unigene data
- Up-regulated: 469 (>2 fold), 1419 (>1.5 fold)
- Down-regulated: 234 (>2 fold), 1108 (>1.5 fold)

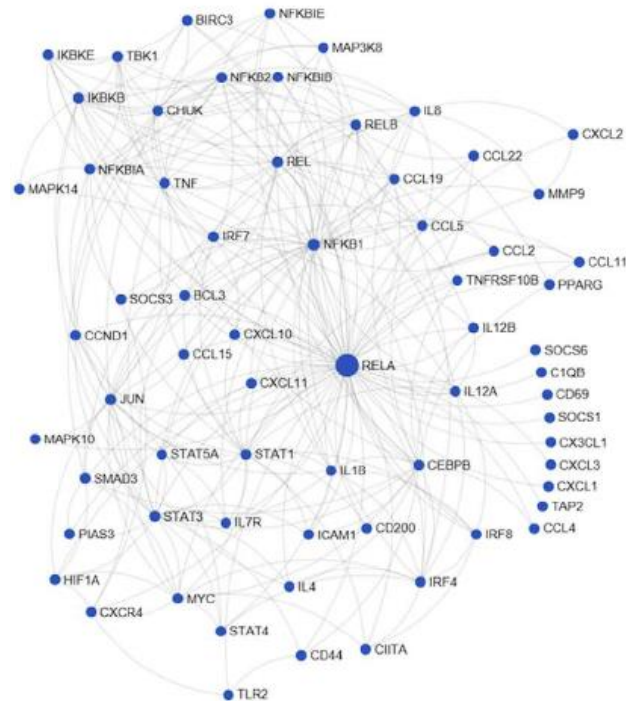
Major clusters of DEGs are altered in tumor-induced DCs



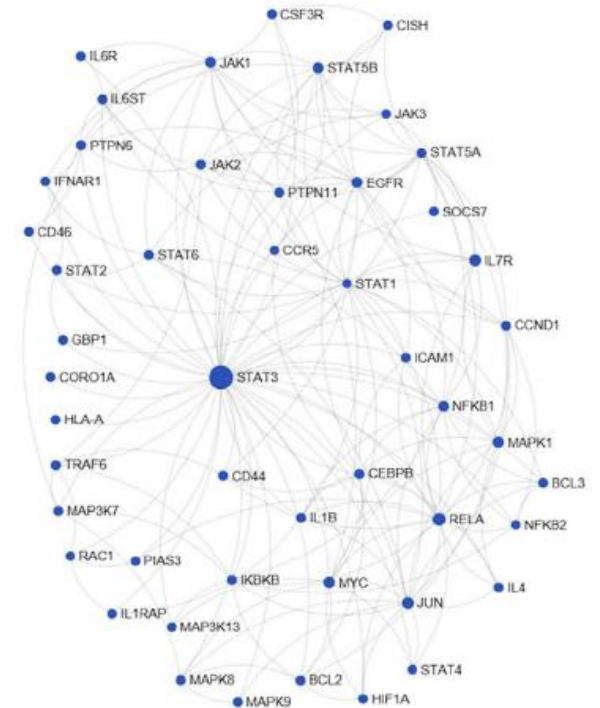
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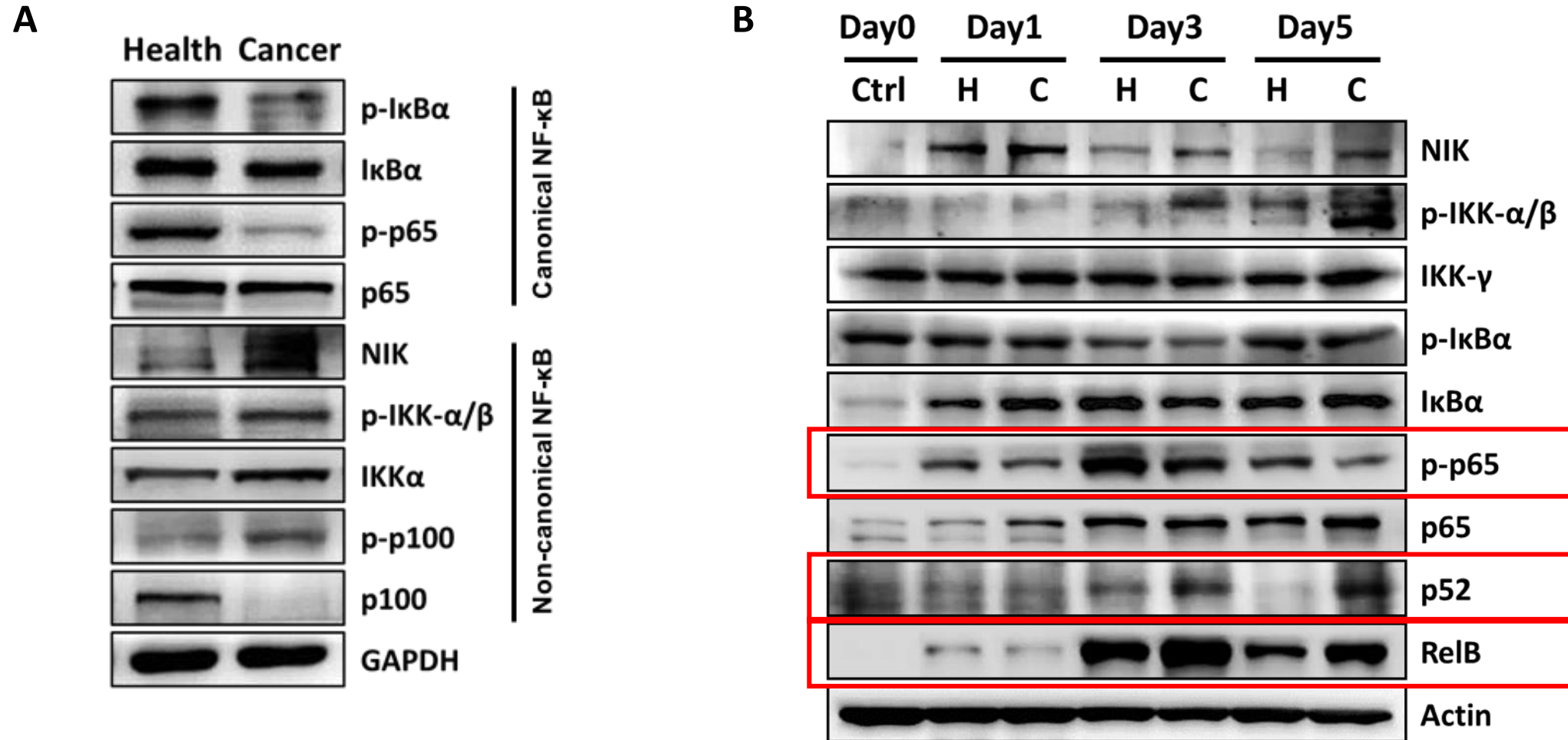
b



C

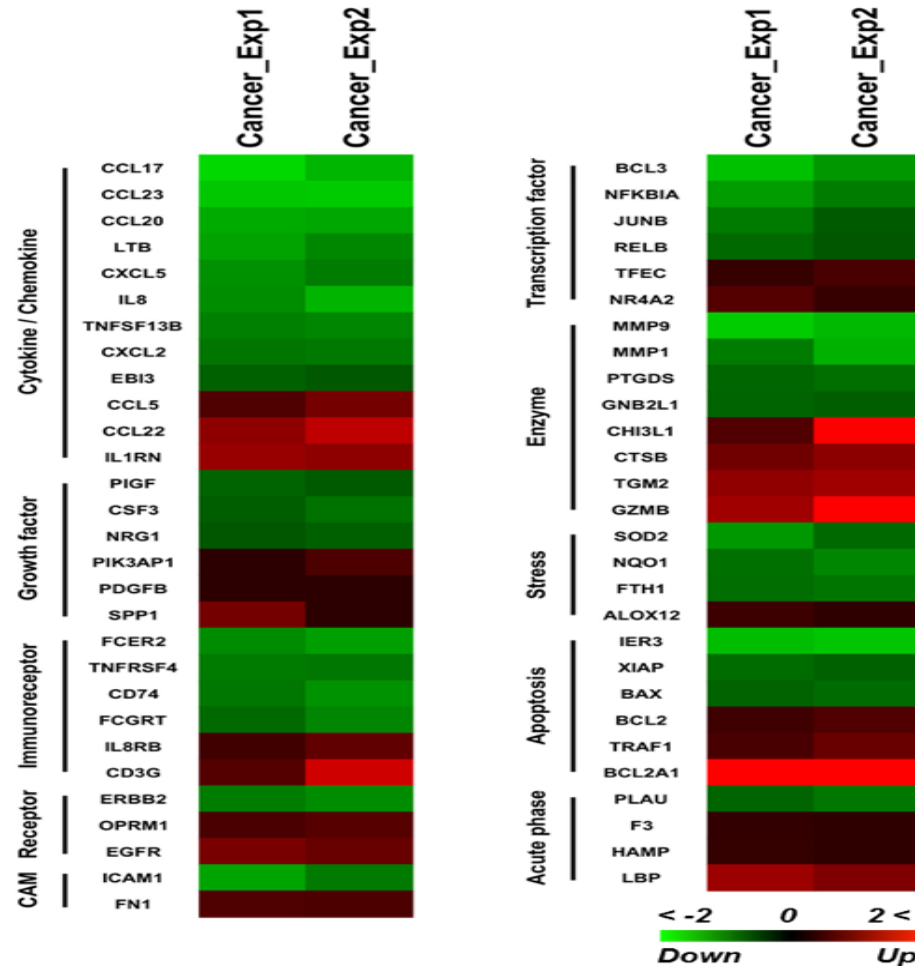


Cancer Suppressed canonical NF- κ B pathway in DC

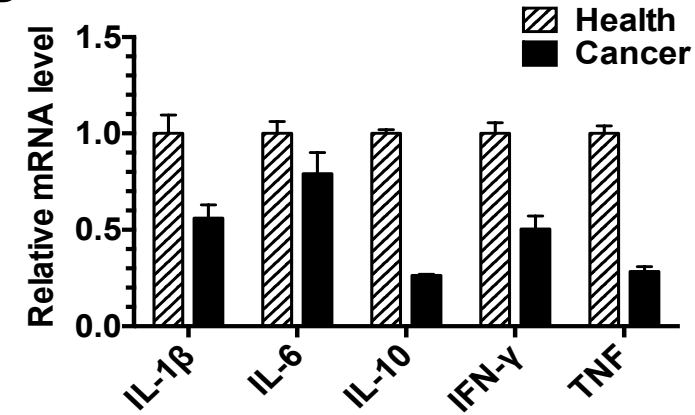


Target genes of canonical NF-κB are altered in tumor-induced DCs

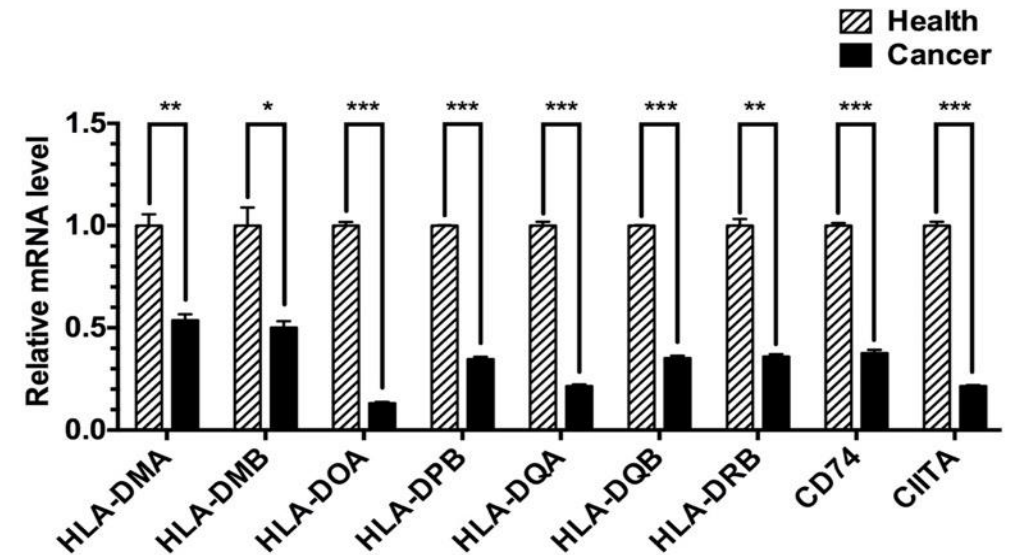
A



B

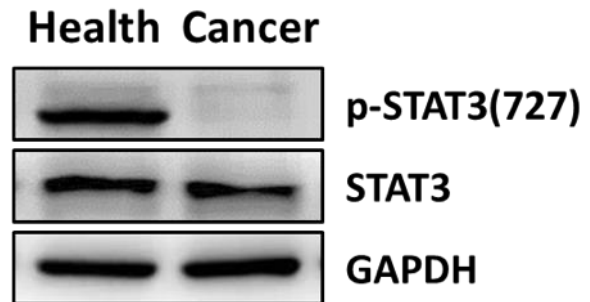


C

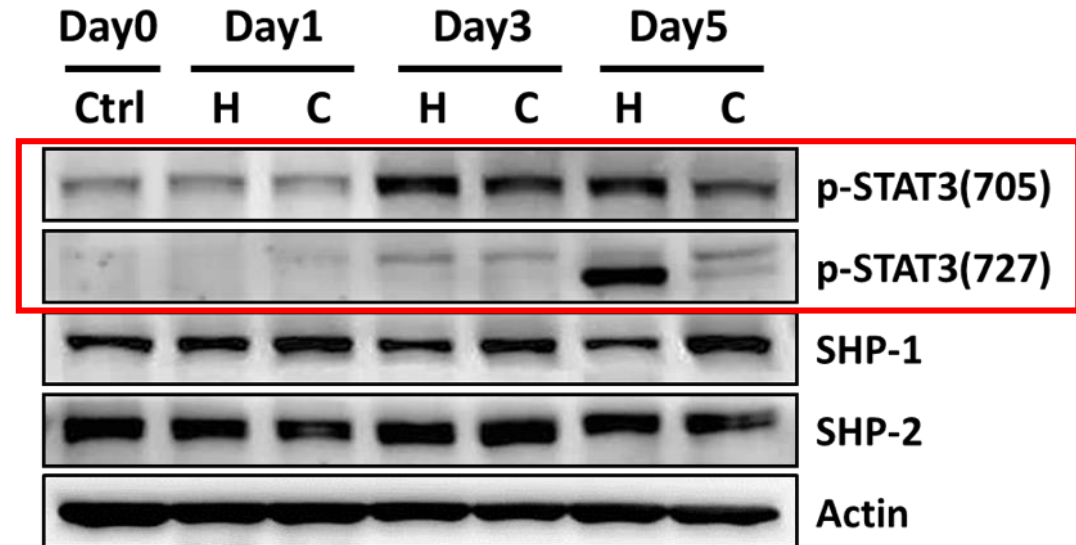


Cancer Suppressed STAT3 pathway in DC

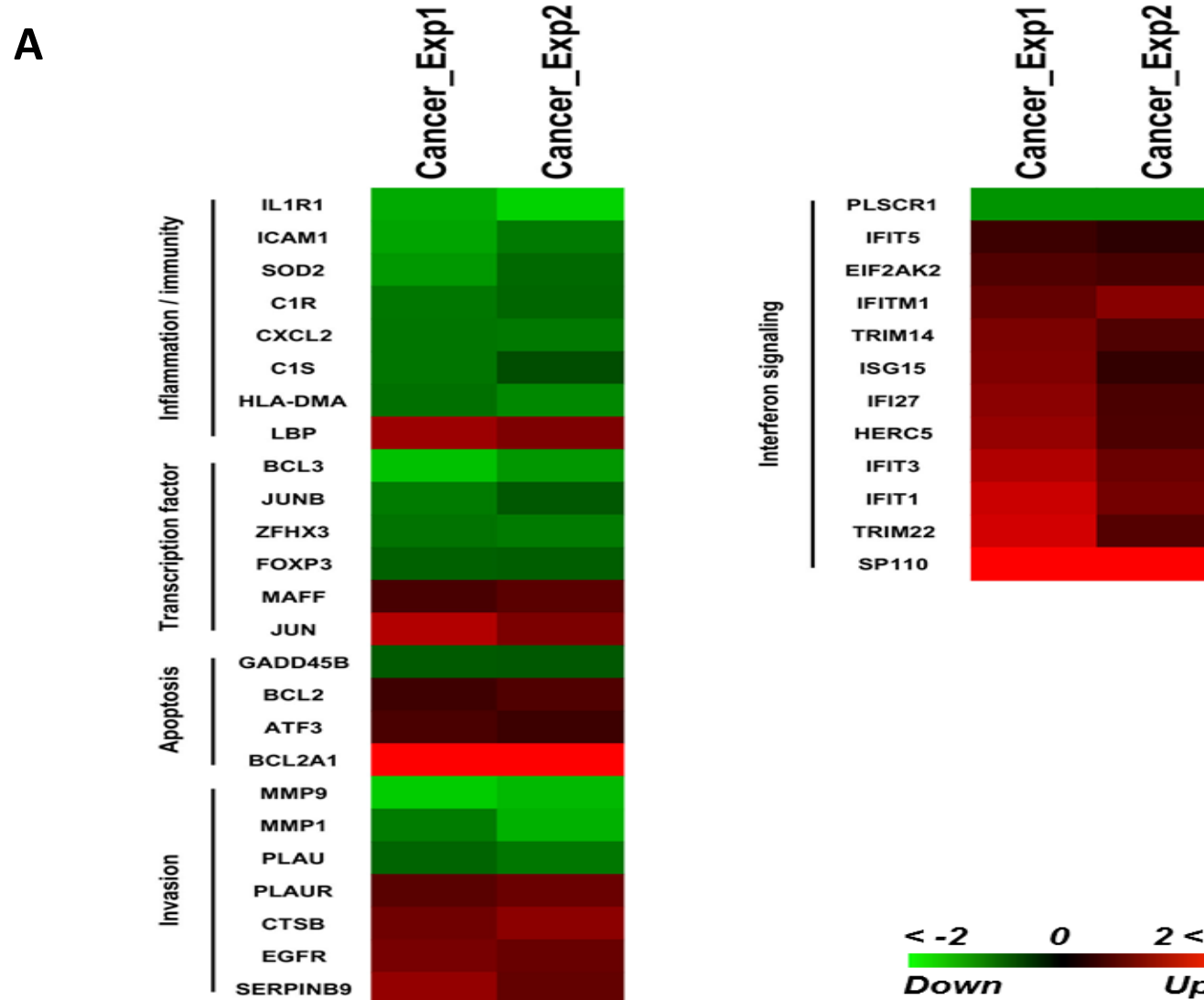
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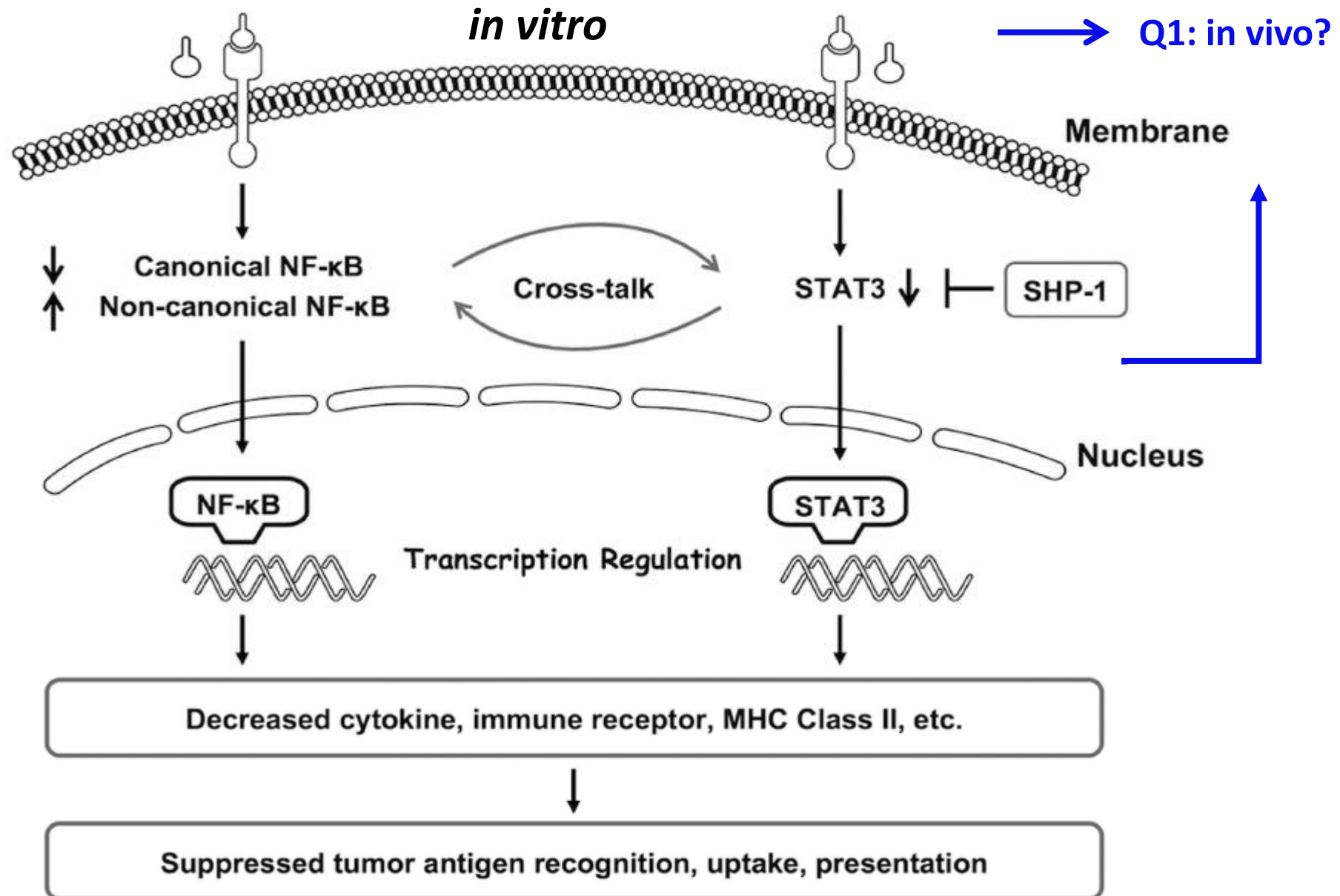


B

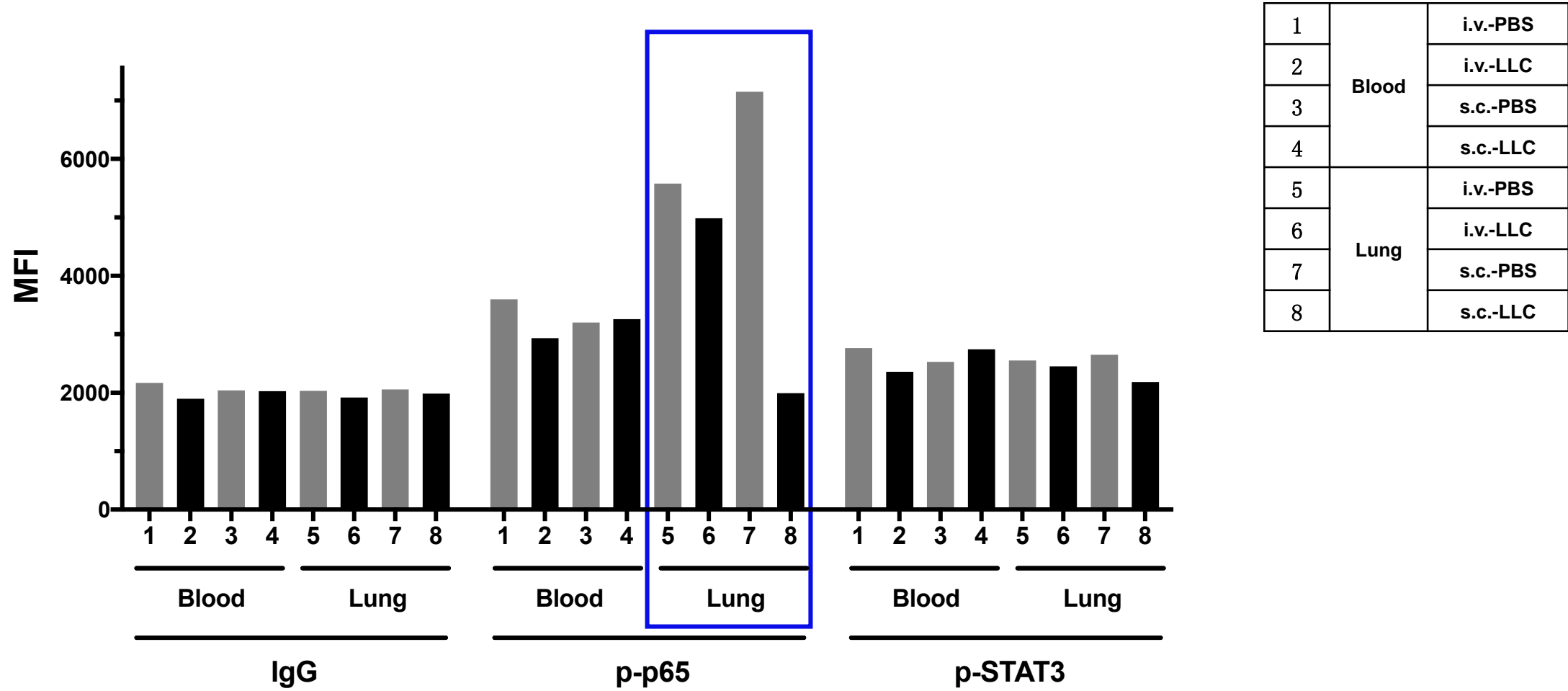


Target genes of STAT3 are altered in tumor-induced DCs



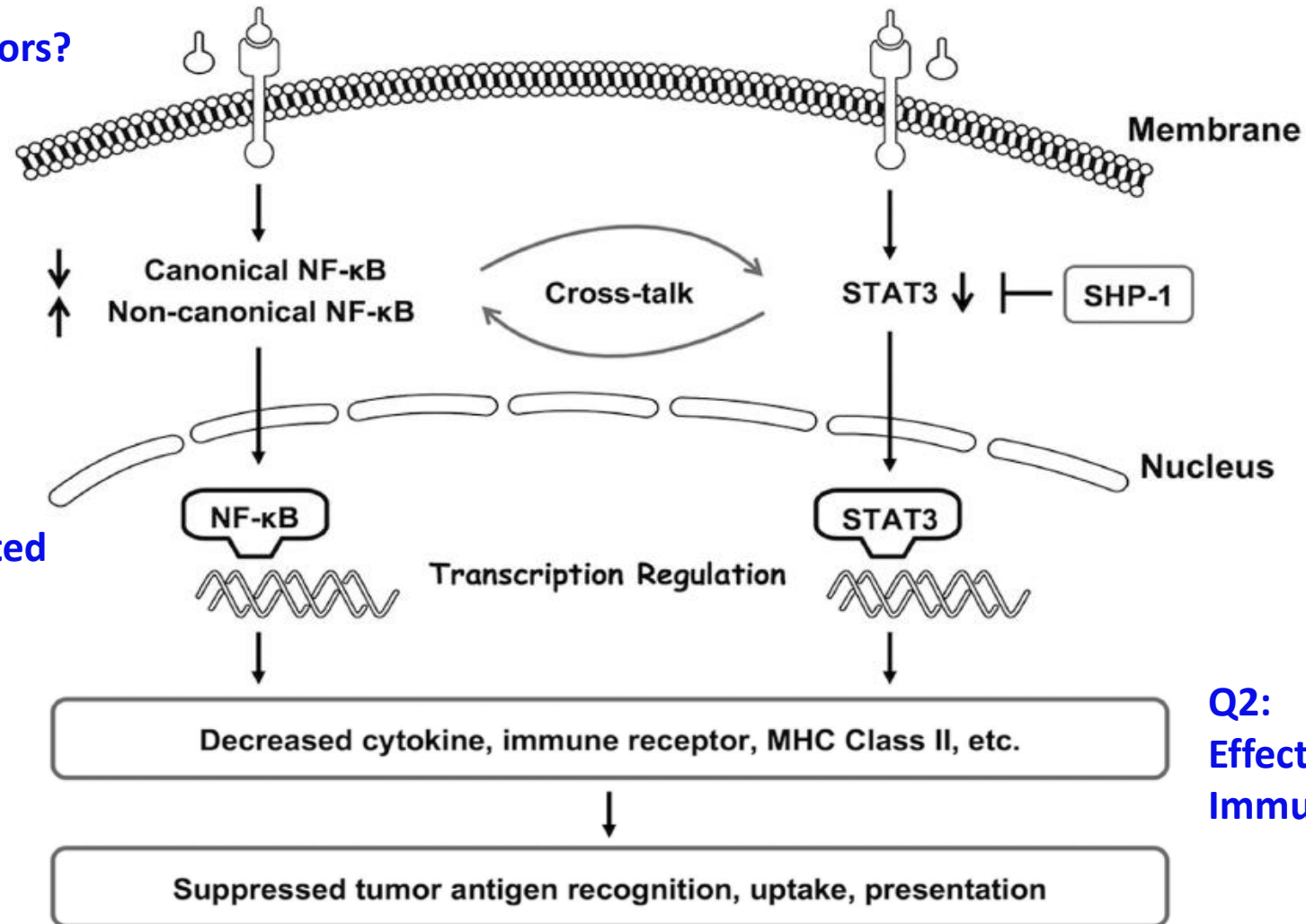


canonical NF-κB pathway was altered in DC in mouse model



1	Blood	i.v.-PBS
2		i.v.-LLC
3		s.c.-PBS
4		s.c.-LLC
5	Lung	i.v.-PBS
6		i.v.-LLC
7		s.c.-PBS
8		s.c.-LLC

Q1: Tumor derived factors?



Q3:
Reversing the deactivated
pathway?

Q2:
Effects to other DC associated
Immune cells?

Lessons and Take Home Messages

- **DC dysfunction is an integrated outcome from tumor environment derived factors stimulus.**