Tumor-suppressive effects of interferon- β through interleukin-24 in melanoma

Yoshinori Watanabe, Munenari Ito, Yoshimasa Nobeyama, Hidemi Nakagawa
Department of Dermatology, The Jikei University School of Medicine, Tokyo, Japan

Introduction

- The IFNs are classified into type I, II and III. (type I: IFN- α , IFN- β · type II: IFN- γ)
E. De Mayer, 1988
- Type I interferon is in widespread use as adjuvant therapy to inhibit melanoma progression.
A.M. Eggermont, 2009
- Feron® maintenance therapy is effective on melanoma.
Yamamoto A, 2014

Purpose

To identify additional molecules to suppress melanoma following treatment with IFN- β

Background

- Our previous study showed that CXCL10 shares the effectiveness of IFN- β on melanoma cells.
- The other suppressive factors have not been elucidated yet.
- Molecules to determine IFN- β sensitivity of melanoma cells have not been identified.

Materials & Methods

Human melanoma cell lines

	Age	Sex
RPMI-7951	18	Female
A375	54	Female
SK-MEL-5	24	Female
G361	31	Male
SK-MEL-1	29	Male

Protein

- Natural-type IFN- β (Tray Medical)

Methods

- Genome-wide micro array
- RT-PCR
- ELISA
- IL-24 knockdown
- Receptor analysis

Results

Wide spectrum of sensitivity to IFN- β in melanoma cells

Genome-wide microarray analysis

List of genes: up-regulated by >5-fold following IFN- β treatment in melanoma cells with high sensitivity to IFN- β (RPMI-7951)
down-regulated by <2-fold in melanoma cells with low sensitivity to IFN- β (SK-MEL-1)

Gene symbol	Description	Fold change	RPMI-7951	SK-MEL-1
XLOC_000027	BROAD Institute lincRNA	32.25	0.69	
GDF15	growth differentiation factor 15	26.02	1.50	
LGALS9	lectin, galactoside-binding, soluble, 9	16.72	1.10	
LOC100131733	uncharacterized LOC100131733	12.19	1.20	
CYP2J2	cytochrome P450, family 2, subfamily J, polypeptide 2	11.86	1.66	
IL24	interleukin 24	9.32	0.80	
CXCL10	chemokine (C-X-C motif) ligand 10	9.13	0.58	
LPAR6	lysophosphatidic acid receptor 6	8.94	0.81	
LMO2	LIM domain only 2	8.02	1.64	
HIST1H2AC	histone cluster 1, H2ac	7.82	1.51	
XLOC_I2_007063	BROAD Institute lincRNA	7.40	1.47	
IDO1	indoleamine 2,3-dioxygenase 1	7.34	0.94	
C15orf48	chromosome 15 open reading frame 48	5.41	1.30	
SPPI	secreted phosphoprotein 1	5.34	1.17	
XLOC_I2_000297	QSD1D6_CERAE (QSD1D6) Guanylate binding protein 1	5.17	1.04	
XLOC_I2_015121	BROAD Institute lincRNA	5.14	0.65	
GMPT	guanosine monophosphate reductase (GMPT)	5.08	1.27

Sensitivity to IFN- β :

RPMI-7951>A375>SK-MEL-5>G361>SK-MEL-1

We chose the secretory proteins from all the candidate genes. In this study, we focused on il-24.

Expression of IL-24 mRNA·protein after treatment with IFN- β : RPMI-7951·A375 >> SK-MEL-5·G361·SK-MEL-1

IL-24 knockdown

Knockdown of IL-24 suppresses the effectiveness of IFN- β .

Receptors: IL-20RA/IL-20RB·IL-22RA/IL-20RB

mRNA expression of IL-24 receptors after treatment with IFN- β : RPMI-7951 >> A375·SK-MEL-5·G361·SK-MEL-1

Interleukin-24

- Discovered by exposing melanoma cells to interferon beta (IFN- β).
Jiang & Fisher, 1993; Jiang et al., 1993, 1995.
- Belongs to the IL-10 family. Jiang, 1995
- Expressed mainly in thymus, spleen, peripheral blood leukocytes and normal melanocytes.
Jiang, 1995
- Activates STAT1 and STAT3 signaling. Menezes, 2014
- Induces cell death in cancer cells without affecting normal cells. Menezes et al. 2014

Conclusions

- IFN- β inhibits melanoma cells in various degrees.
- IL-24 is expressed in melanoma cells in the order of their sensitivity to IFN- β
- Knockdown of IL-24 suppresses the effectiveness of IFN- β .