

Involvement of TLR4/STAT3 signaling in the antimelanoma effects of atractylenolide II

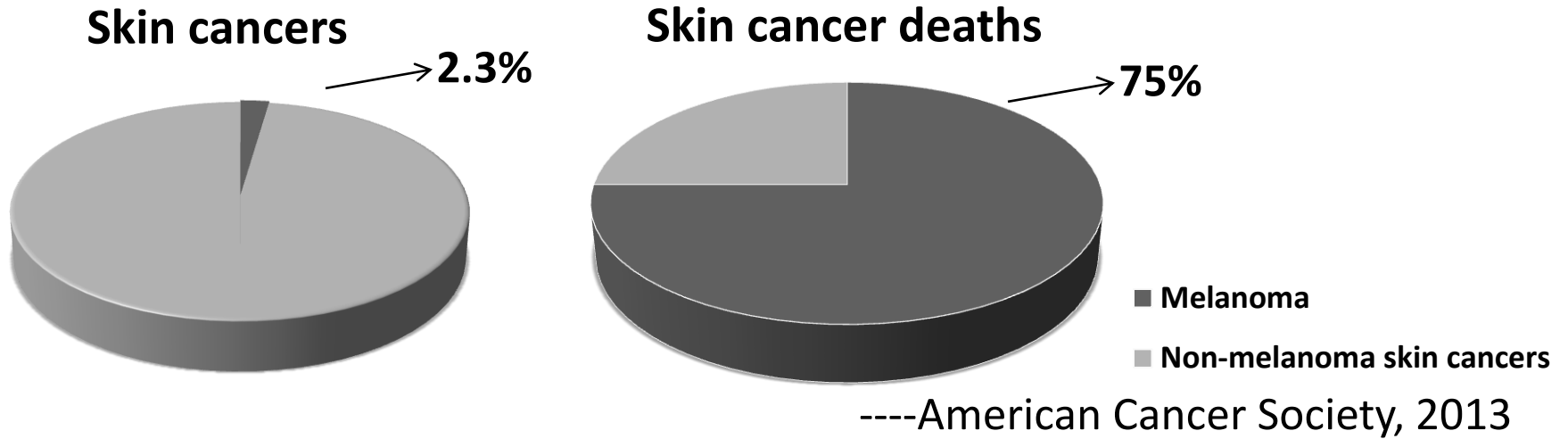
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School of **中醫藥學院**
Chinese Medicine

Melanoma fact



The incidence of melanoma has increased **15 times** in the last 40 years. This is a more rapid increase than any other cancer.

----*Aim at Melanoma Org.* 2015



Drugs approved for treating melanoma

Dacarbazine

DTIC-Dome (Dacarbazine)

Dabrafenib

Vemurafenib

Tafinlar (Dabrafenib)

Zelboraf (Vemurafenib)

Pembrolizumab

Mekinist (Trametinib)

Trametinib

Aldesleukin (IL-2)

Intron A (Recombinant Interferon Alfa-2b)

Ipilimumab

Keytruda (Pembrolizumab)

Nivolumab

Opdivo (Nivolumab)

Peginterferon Alfa-2b

PEG-Intron (Peginterferon Alfa-2b)

Proleukin (Aldesleukin)

Recombinant Interferon Alfa-2b

Sylatron (Peginterferon Alfa-2b)

Yervoy (Ipilimumab)

BRAF inhibitors

MEK inhibitors

Immunotherapy drugs

Low response

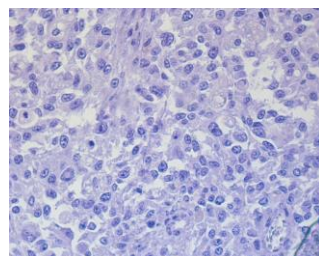
Acquired drug resistance

High cost

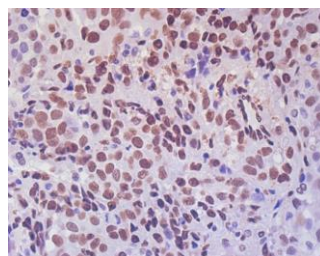
Associated toxicity

Novel targeted therapies for melanoma are still needed

Signal transducer and activator of transcription 3 (STAT3) is activated in melanoma



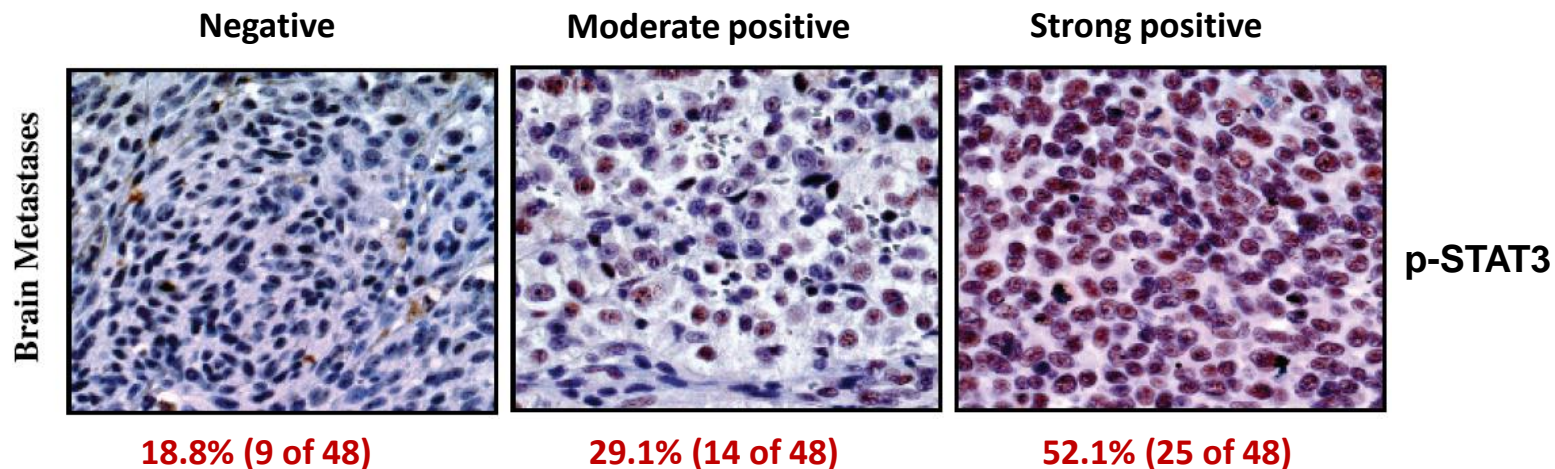
Normal



Melanoma

**p-STAT3
(Tyr705)**

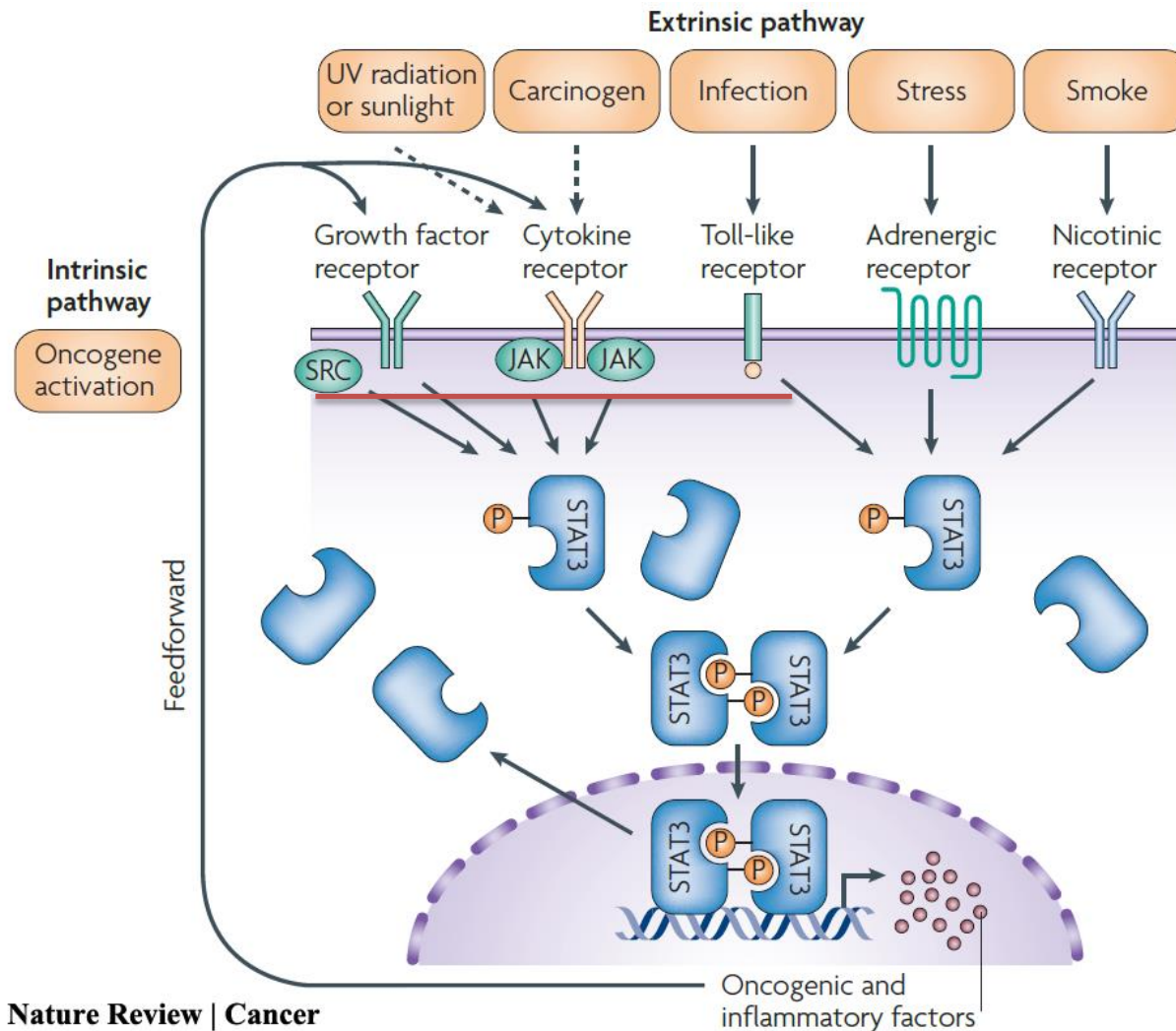
-----*Oncotarget*. 2012;3:336-344.



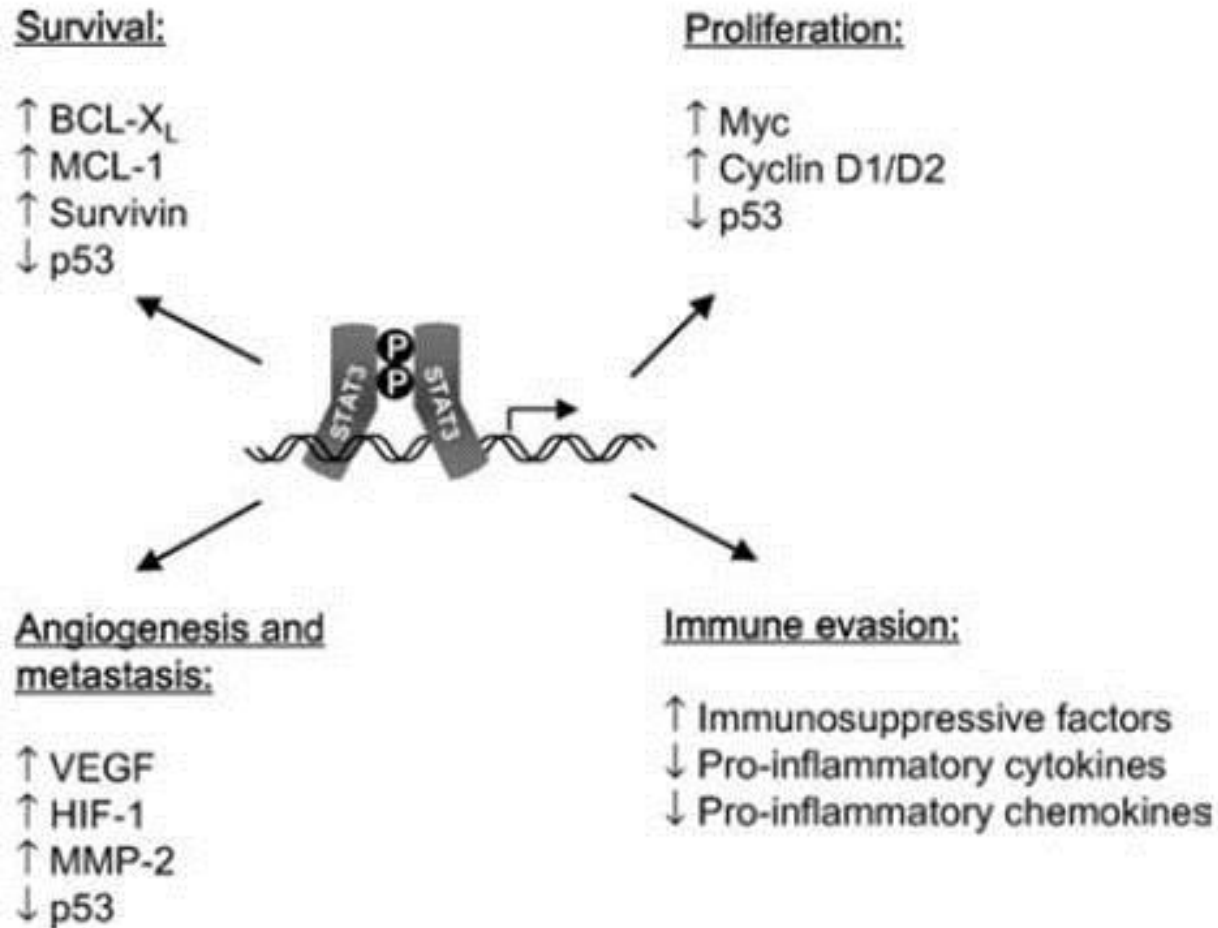
48 Human melanoma brain metastasis specimens

-----*Cancer Res*. 2006;66:3188-96.

STAT3 can be activated by extrinsic and intrinsic pathways



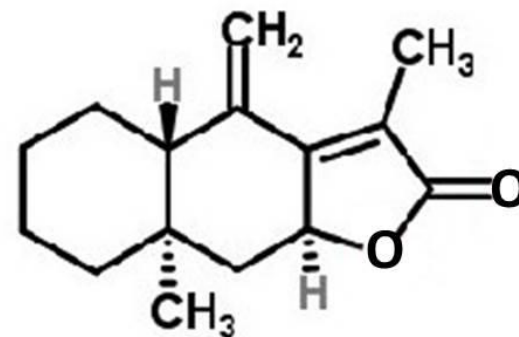
Role of constitutively activated STAT3 in melanoma



Sesquiterpenes that suppress STAT3 signaling and exhibit anticancer activities

Compound	Cancer	Reference
Zerumbone	Breast cancer	<i>Oncol Rep.</i> 2014;32:2666-72.
Bigelovin	Liver cancer	<i>Acta Pharmacol Sin.</i> 2015;36:507-16.
Xanthatin	Non-small cell lung cancer	<i>PLoS One.</i> 2013;8:e81945
Parthenolide	Lung cancer	<i>Curr Cancer Drug Targets.</i> 2014 ;14:59-69.
	Liver cancer	<i>J Cell Physiol.</i> 2011;226:1632-41.
	Prostate cancer	<i>Prostate.</i> 2009;69:827-37.
Germacrone	Liver cancer	<i>J Huazhong Univ Sci Technolog Med Sci.</i> 2013 ;33:339-45.
Alantolactone	Liver cancer	<i>Biomed Res Int.</i> 2013;2013:719858.
Brevilin A	Lung cancer	<i>PLoS One.</i> 2013 ;8:e63697.

Atractylenolide II (AT-II) is a sesquiterpene compound isolated from *Baizhu*



Atractylenolide II (AT-II) :
A sesquiterpene

Atractylodis Macrocephalae Rhizoma (*Baizhu*)

***Baizhu* is commonly prescribed in melanoma management**

Sesquiterpene containing volatile oil from *Baizhu*

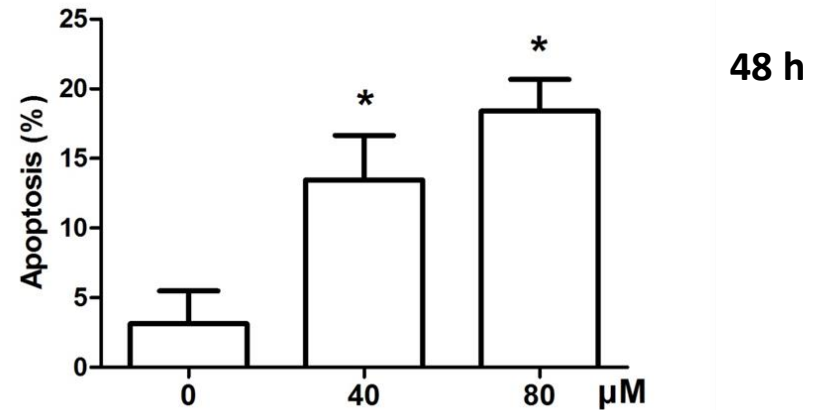
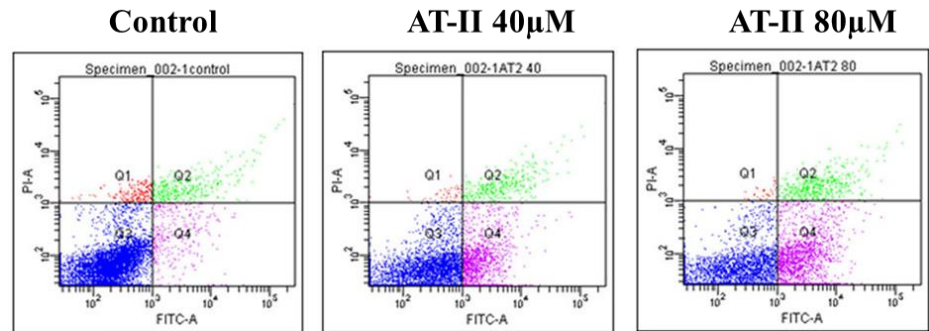
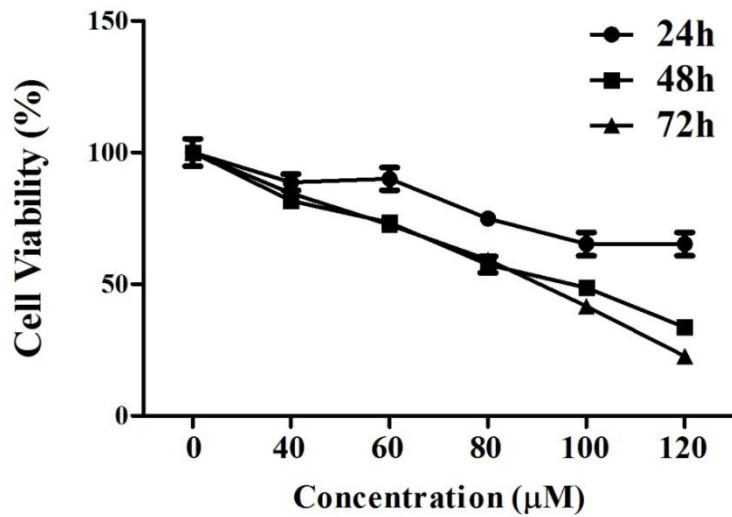
- has **no chronic toxicity** in rats
- shows beneficial effects in cancer cachexia **patients without overt side effects**
- Good oral bioavailability** in rats

-----A review on the anti-tumor activities of Atractylodis Macrocephalae Rhizoma and formulas contain this herb. *Zhongguo Zhong Yi Yao Xin Xi Za Zhi*. 2004

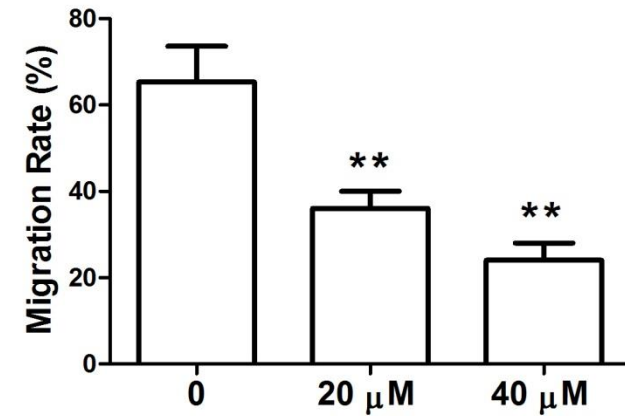
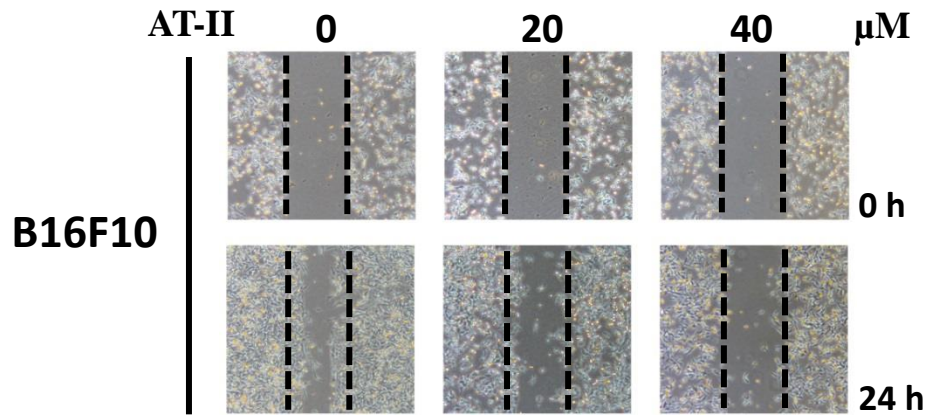
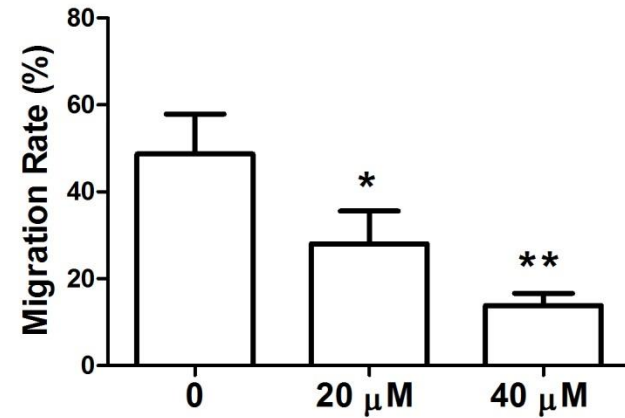
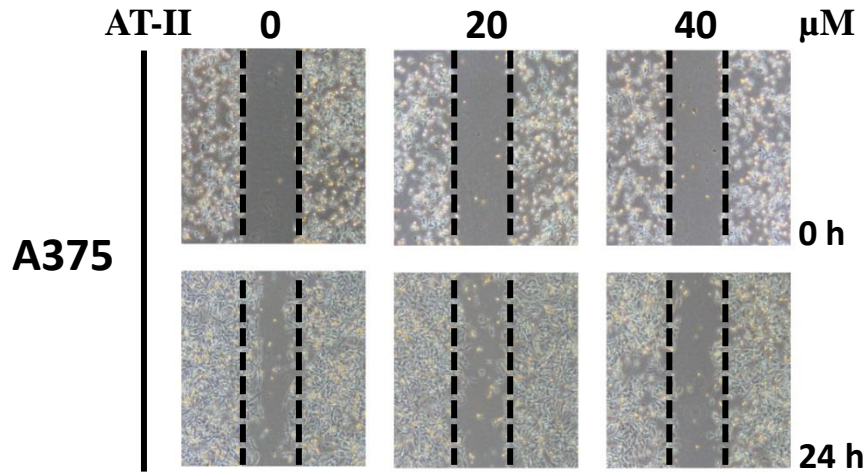
-----A case report for the treatment of melanoma systemic metastasis using Chinese medicine. *Zhongguo Min Jian Liao Fa*. 2008

-----Successful treatment of malignant melanoma. *Shang Hai Zhong Yi Yao Za Zhi*. 2005

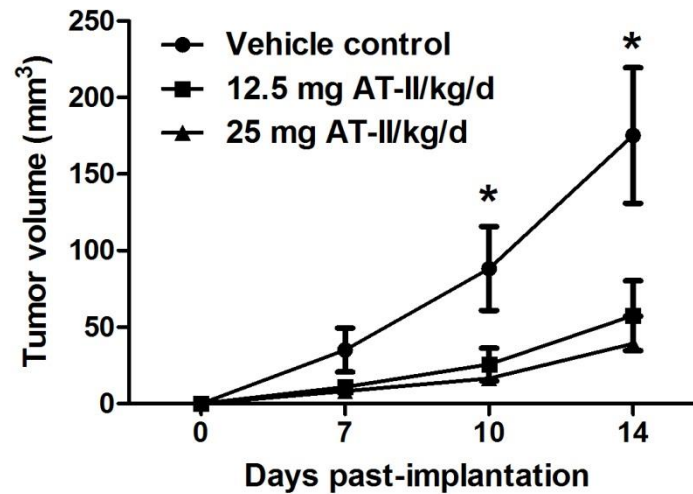
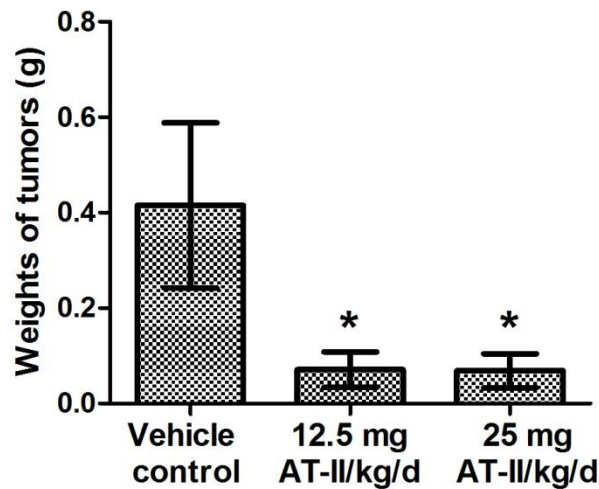
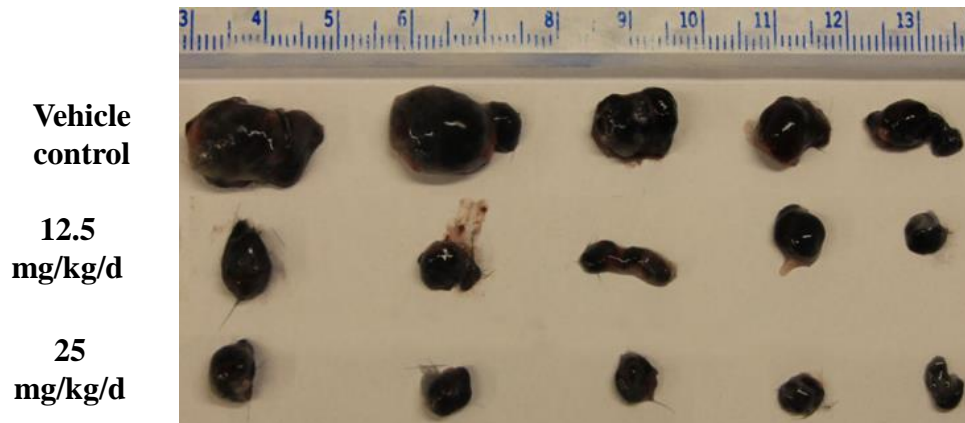
AT-II decreased the viability and induced apoptosis of A375 human melanoma cells



AT-II inhibited the migration of A375 and B16F10 cells



AT-II inhibited tumor growth in B16 melanoma-bearing mice

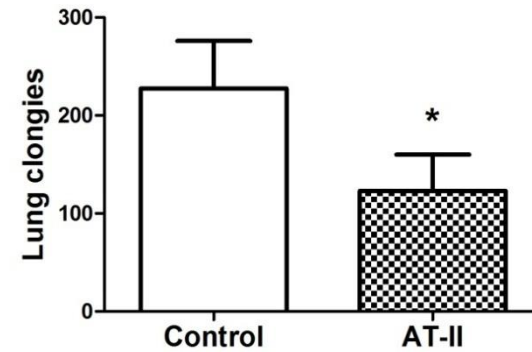
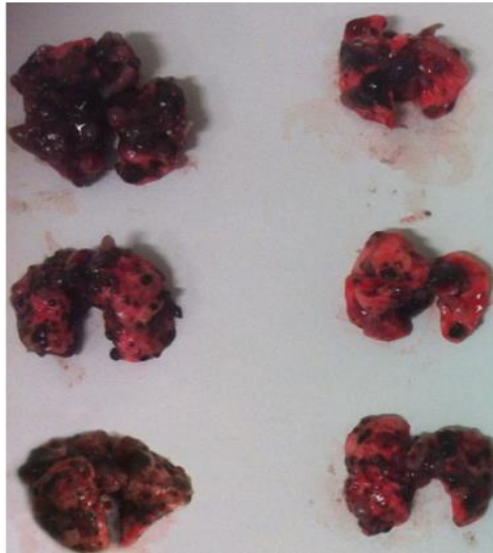


----*Exp Dermatol.* 2014 ;23:855-7.

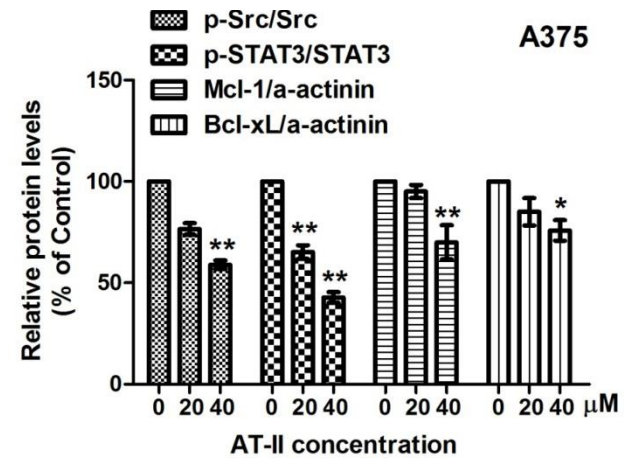
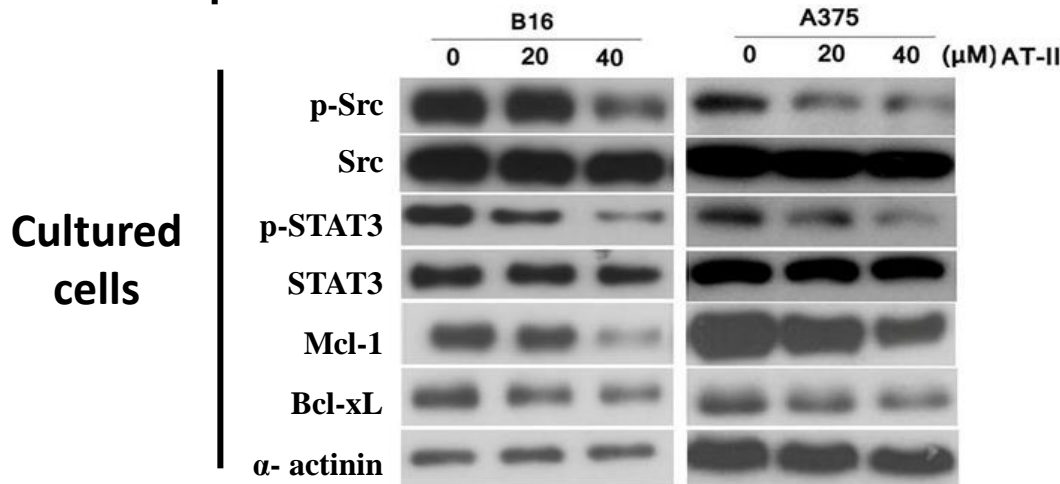
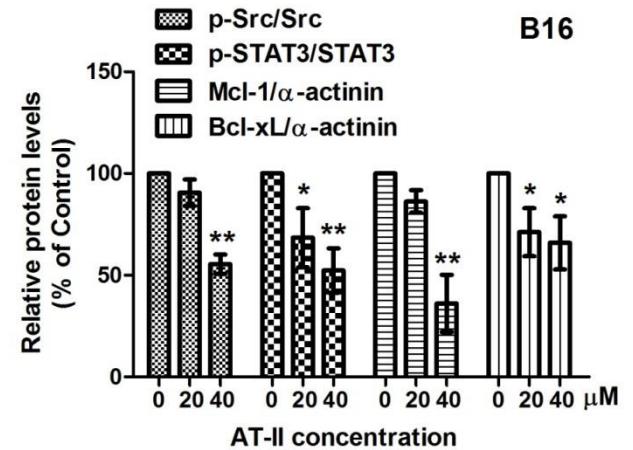
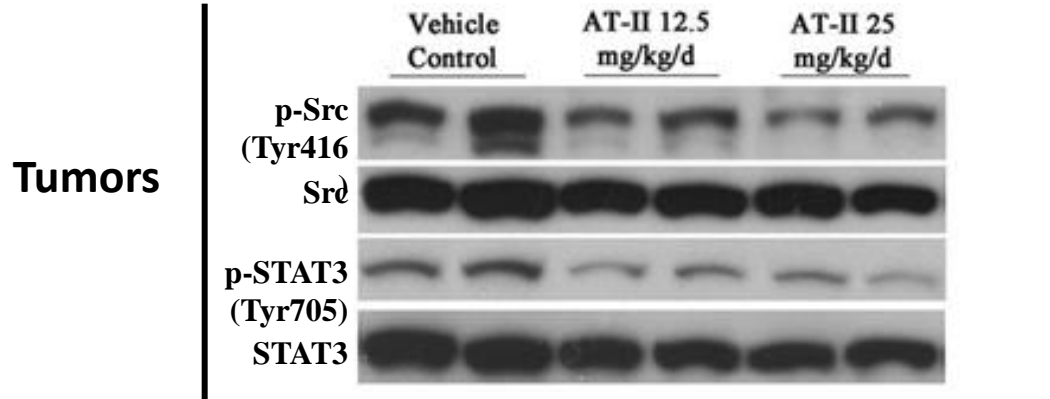
AT-II decreased B16F10 melanoma cell lung metastasis

Vehicle
control

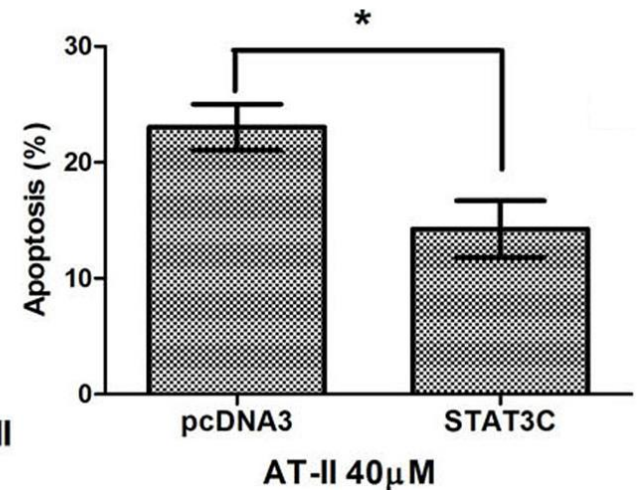
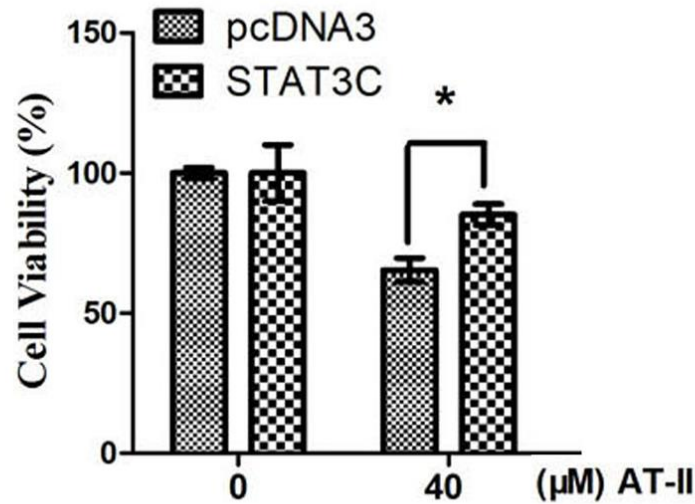
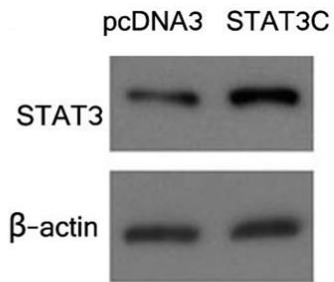
AT-II 12.5
mg/kg/d



AT-II inhibited STAT3 signaling in B16 tumors and melanoma cultured cell

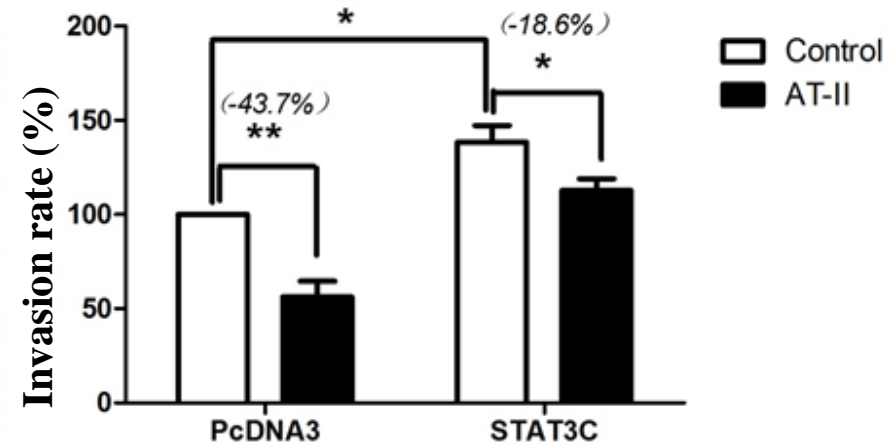
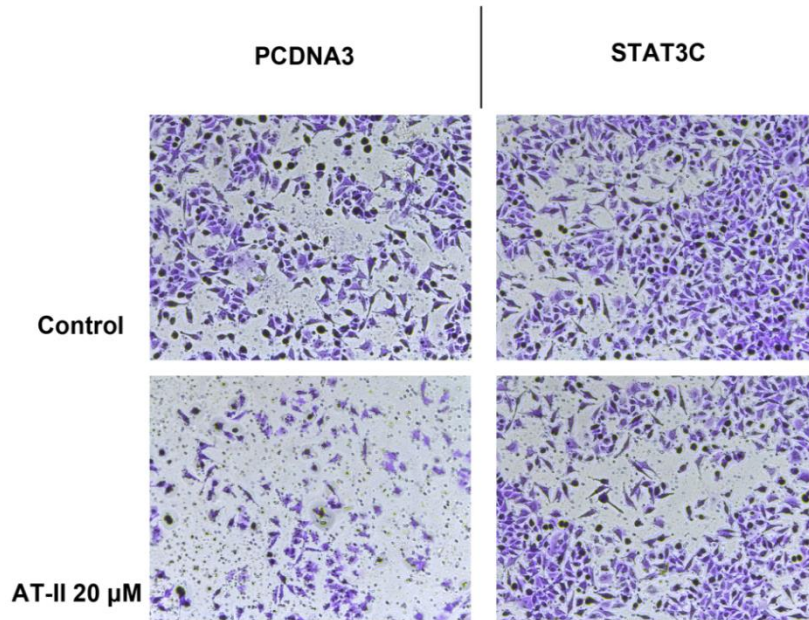


Overexpression of STAT3C diminished the effects of AT-II on cell growth inhibition and apoptosis induction in A375 cells



----*Exp Dermatol.* 2014;23:855-7.

Overexpression of STAT3C diminished the effects of AT-II on inhibiting A375 cells invasion



Activation of TLR4 signaling promotes melanoma progression

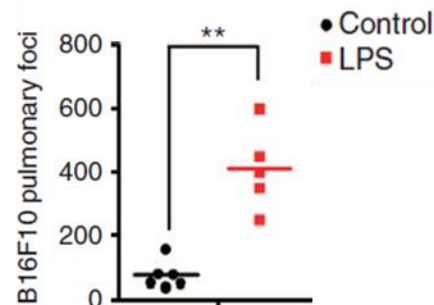
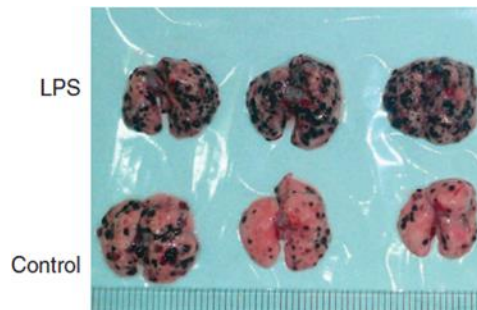
LPS activate TLR4/NF- κ B to induce EMT of melanoma in a mouse model.

----*Innate Immun.* 2012 ;18:685-93.

TLR4 signaling promotes the migration of human melanoma cells.

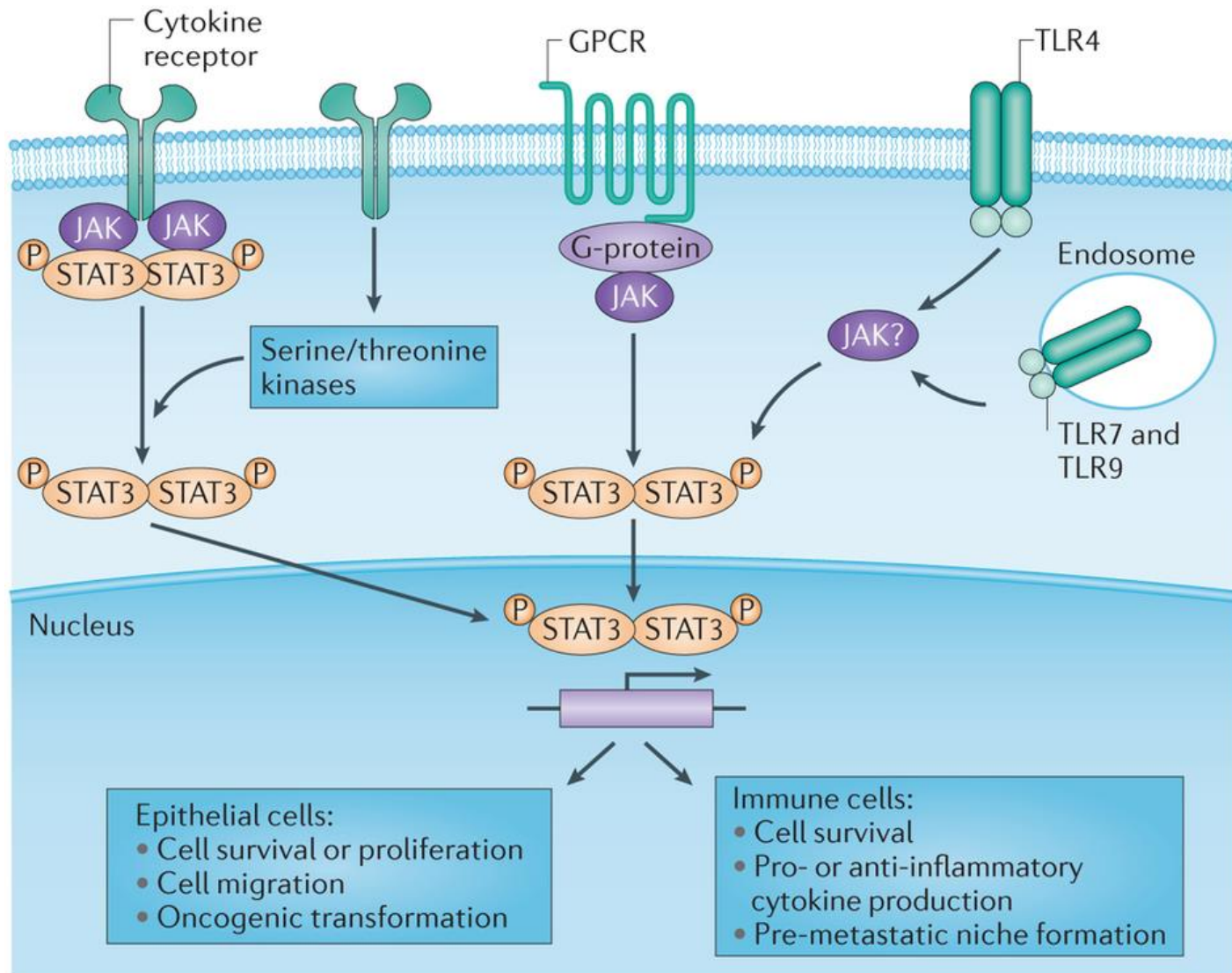
----*Tohoku J Exp Med.* 2014;234:57-65.

Activation of TLR4 promotes melanoma metastasis in mice.



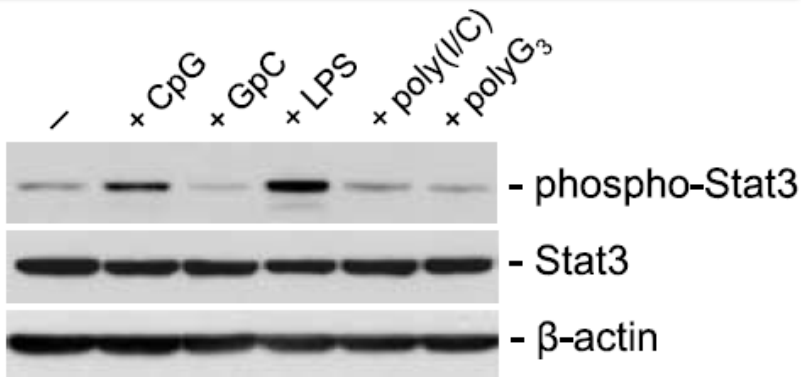
----*Nat Commun.* 2014;5:5256.

TLR4 mediates STAT3 activation



TLR4 mediates STAT3 activation in different cell types

- LPS activates STAT3 in splenic dendritic cells (DCs).



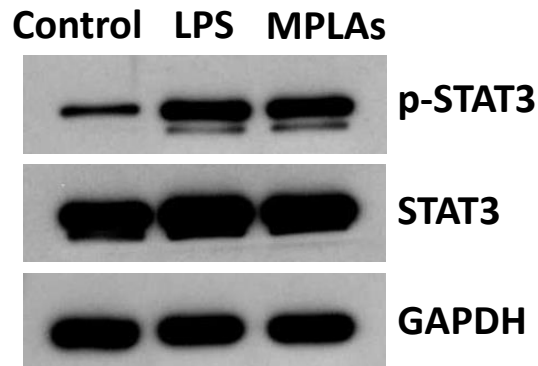
----*Cancer Res.* 2009;69(6):2497-505.

- Increased TLR4 expression in intestinal epithelial cells activates STAT3 to promote colon tumor growth in mice.

----*Nat Rev Cancer.* 2014;14(11):736-46.

- TLR4 mediates STAT3 activation and increases IL-6 and IL-10 secretion in bladder epithelial cells.

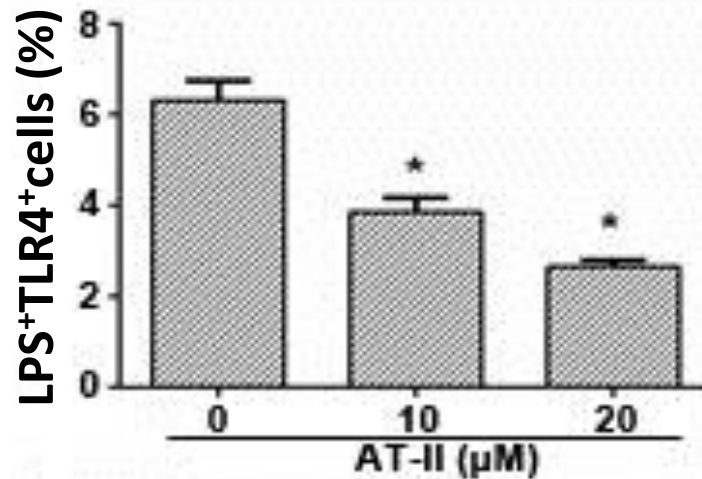
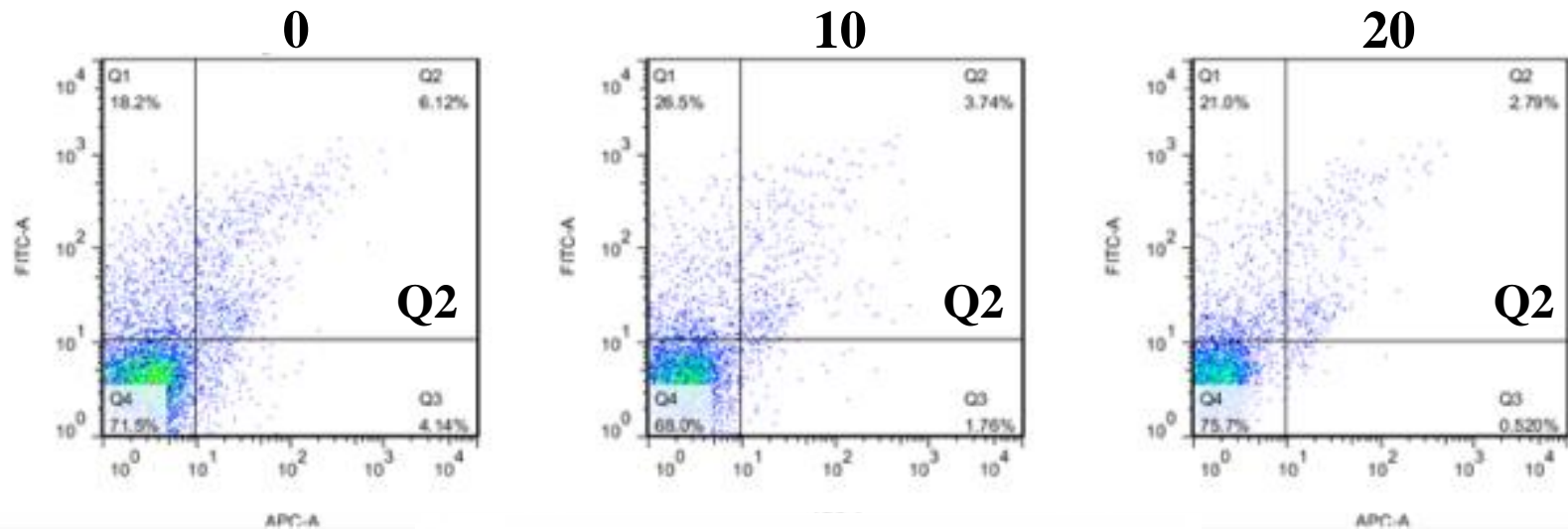
----*Inflammation.* 2013;36:1064-74.



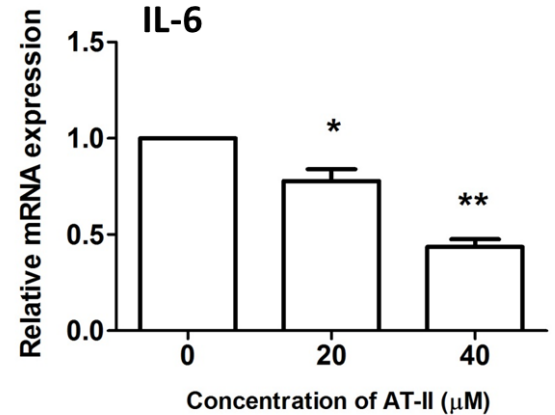
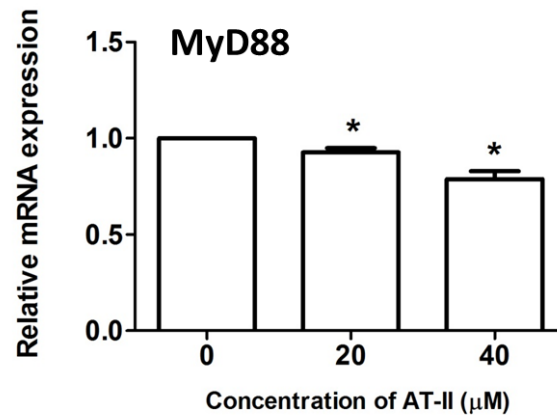
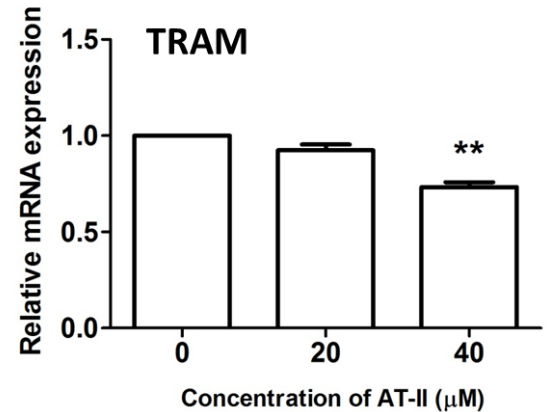
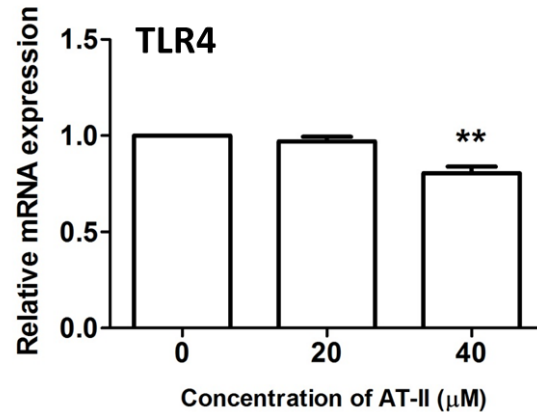
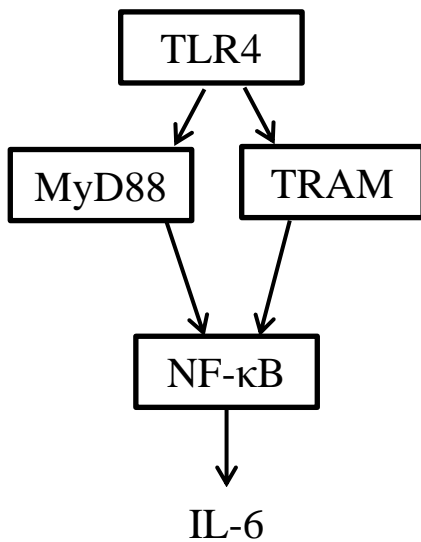
- LPS and MPLAs (a TLR4 agonist) activate STAT3 in A375 human melanoma cells.

AT-II reduced LPS binding to TLR4 in A375 cells

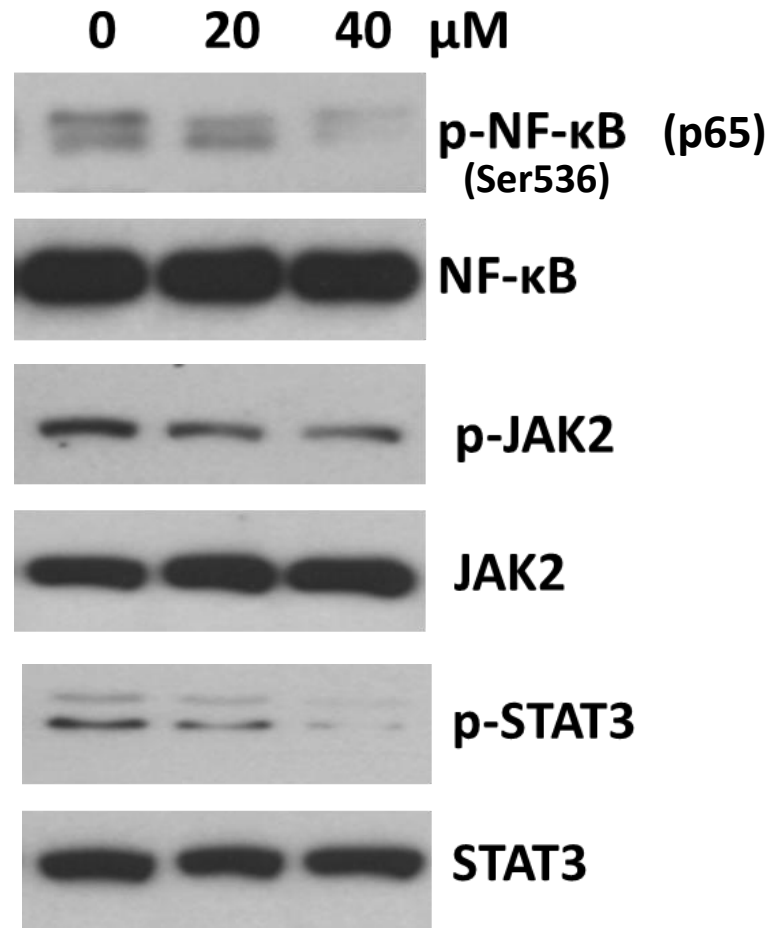
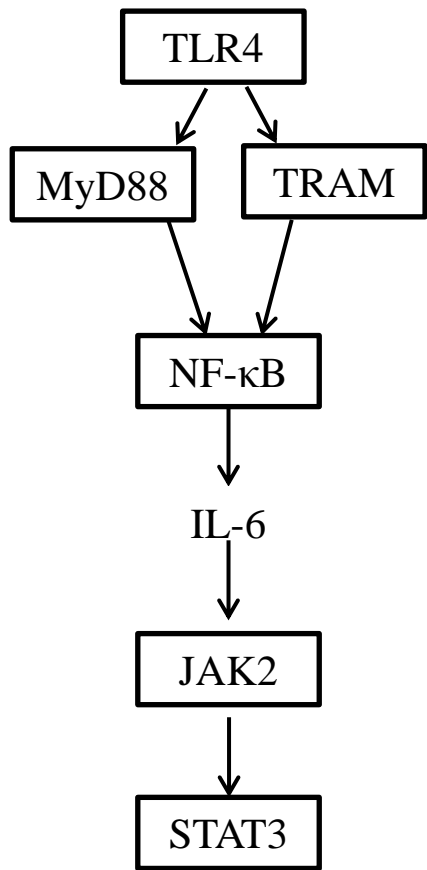
AT-II (μM)



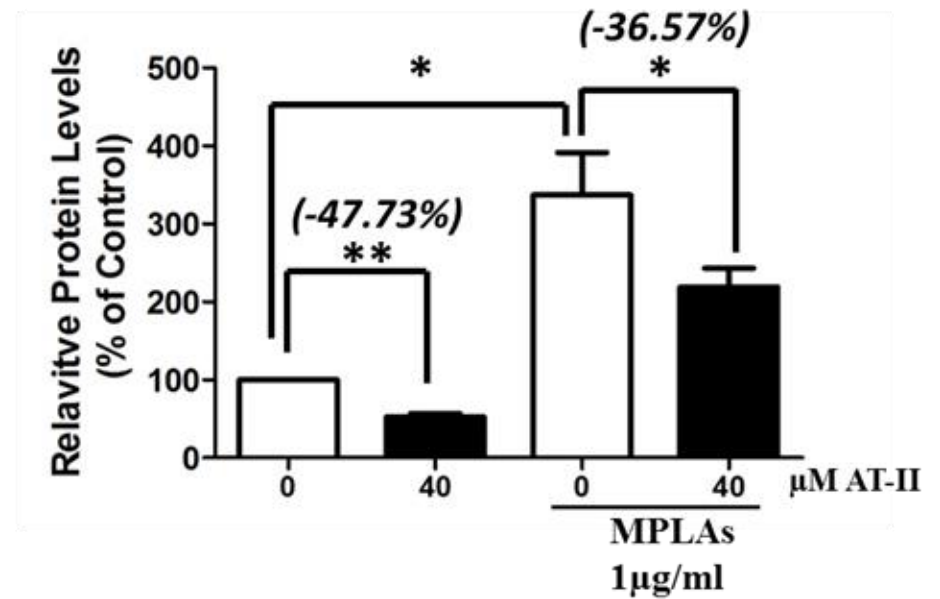
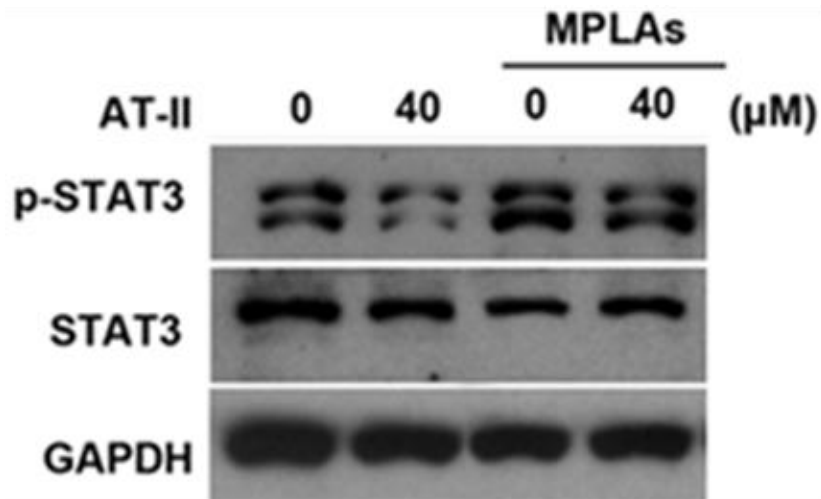
AT-II downregulated mRNA expression levels of TLR4 signaling molecules in A375 melanoma cells



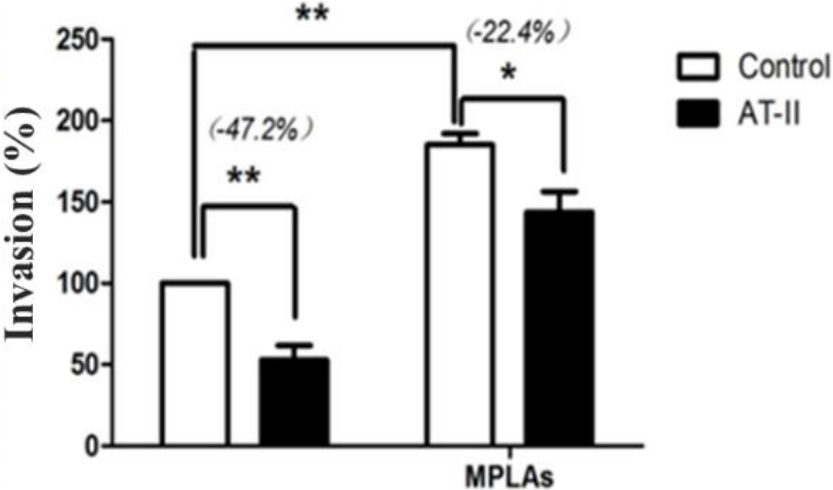
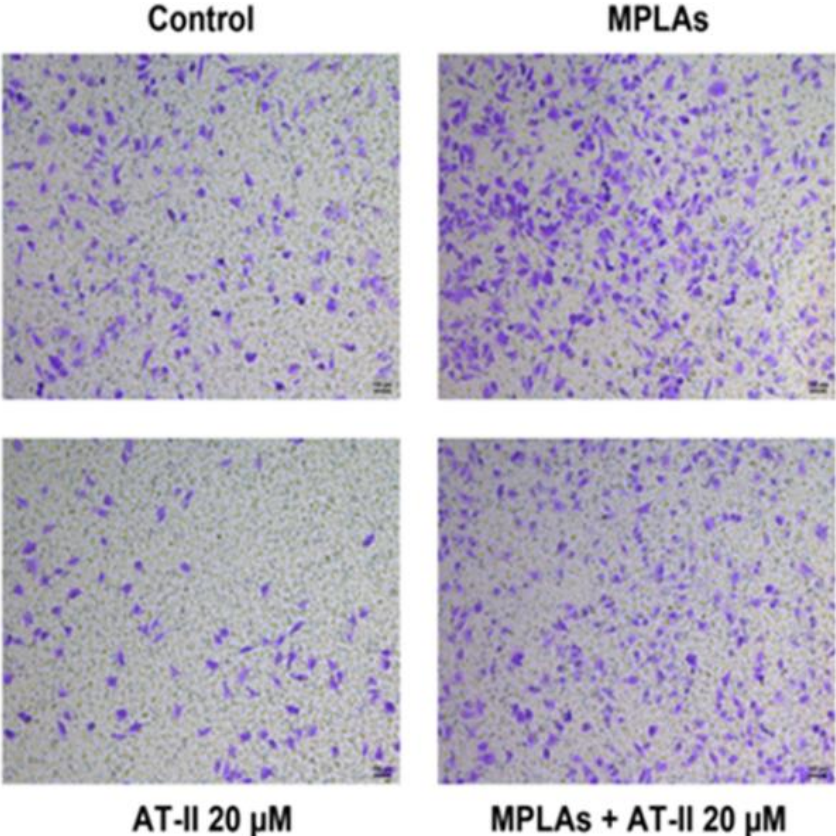
AT-II inhibited the activities of TLR4 signaling molecules in A375 melanoma cells



TLR4 activation diminished the inhibitory effects of AT-II on STAT3 phosphorylation in A375 cells

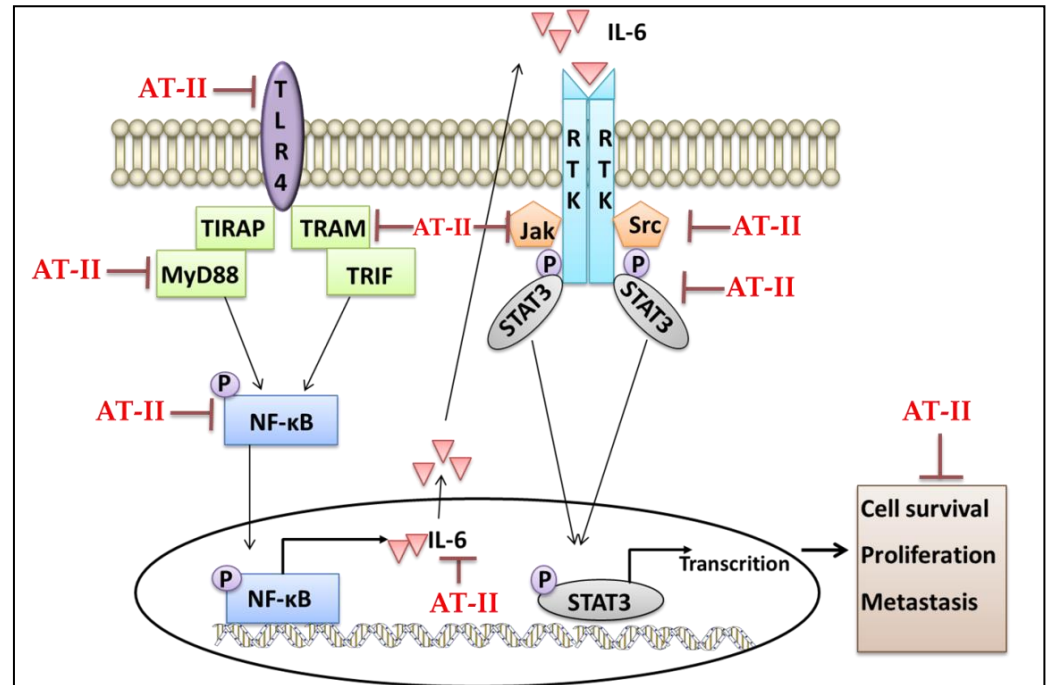


TLR4 activation diminished the invasion-inhibitory effect of AT-II in A375 cells



Summary

1. AT-II exerted *in vitro* and *in vivo* antimelanoma activities.
2. AT-II downregulated STAT3 signaling in B16 tumors and melanoma cultured cells.
3. AT-II inhibited TLR4 signaling in A375 cells.
4. Overexpression of STAT3C diminished the effects of AT-II on cell growth inhibition, apoptosis induction and invasion inhibition in A375 cells.
5. TLR4 activation diminished the inhibitory effects of AT-II on STAT3 phosphorylation and cell invasion in A375 cells.



Inhibition of TLR4/STAT3 signaling contributes to the antimelanoma effects of AT-II.

Our research team



Thank you!



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2016/17



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APPLICATION DEADLINE: Dec. 1, 2015

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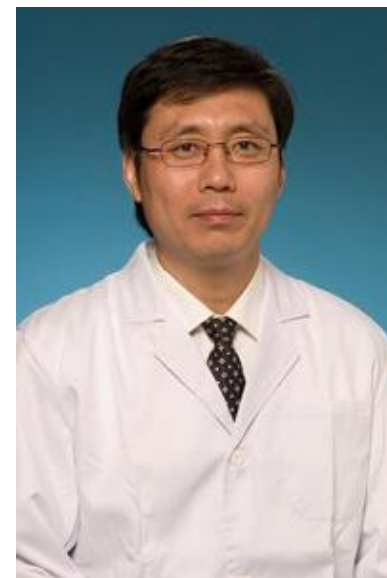
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Melanoma Cell Growth by Activating the
Akt Signaling Pathway**
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Hui Yee Kwan^{†1}, Xiuqiong Fu[‡], Bin Liu[§], Xiaojuan Chao[‡],
Chi Leung Chan[‡], Huihui Cao[‡], Tao Su[‡], Anfernee Kai Wing Tse[‡],
Wang Fun Fong[‡] and Zhi-Ling Yu^{‡2}

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Volume 87, Issue 3, 1 February 2014, Pages 424–434



Quercetin exerts anti-melanoma activities and inhibits STAT3
signaling

Hui-Hui Cao, Anfernee Kai-Wing Tse, Hui-Yee Kwan, Hua Yu, Chi-Yan Cheng, Tao Su, Wang-Fun Fong,
Zhi-Ling Yu 