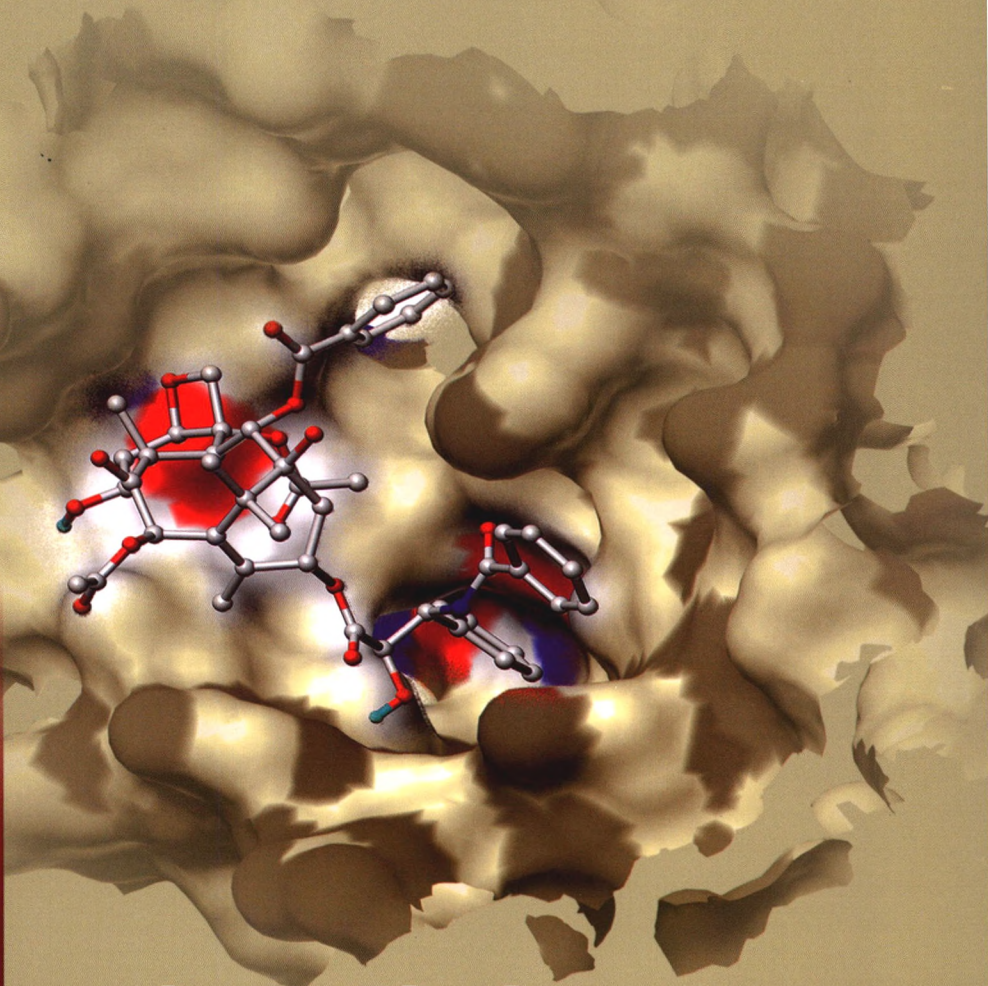


药 学 学 报

第54卷

第10期

2019 Vol. 54 No. 10



Acta Pharmaceutica Sinica

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万方数据

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化疗药调控肿瘤免疫应答机制研究进展



中国药学会
中国医学科学院药物研究所

药 学 学 报

第 54 卷 第 10 期 2019 年 10 月

肿瘤免疫药物治疗现状与对策专刊

图 文 摘 要

综述

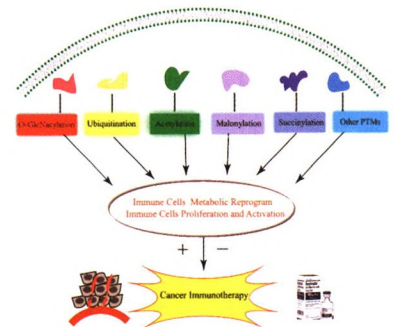
1711

蛋白翻译后修饰与肿瘤免疫治疗

金晶, 季鸣, 陈晓光*

(中国医学科学院、北京协和医学院药物研究所, 天然药物活性物质与功能国家重点实验室/创新药物非临床药物代谢及 PK/PD 研究北京市重点实验室, 北京 100050)

蛋白质翻译后修饰对肿瘤微环境中免疫细胞的增殖、活化以及代谢重编程等都有重要影响, 这或为肿瘤免疫治疗提供新的思路。



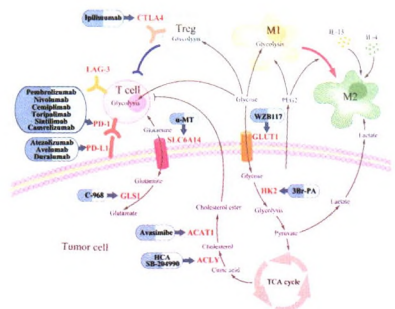
1718

肿瘤免疫和代谢药物靶点研究进展

刘金宜, 任利文, 李莎, 唐琴, 李婉, 郑湘锦, 王金华*, 杜冠华*

(中国医学科学院、北京协和医学院药物研究所, 药物靶点研究与新药筛选北京市重点实验室, 北京 100050)

肿瘤免疫微环境和肿瘤代谢微环境对肿瘤的发生发展和转移起着重要作用。本文对近年来肿瘤免疫和肿瘤代谢的相关药物靶点研究进展及药物开发进展以及面临的一些问题进行了综述。



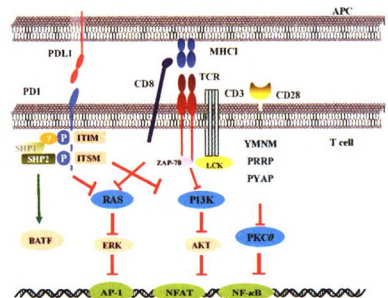
1728

PD-1/PD-L1 免疫治疗在肿瘤中的耐药机制和研究进展

严时佳, 孙蕾, 万国辉*

(中山大学药学院, 广东 广州 510006)

PD-1/PD-L1 免疫检查点抑制剂是当前癌症免疫治疗的重要手段, 但其响应率较低和耐药的出现, 限制了此类药物的进一步应用发展。发现更有效的癌症治疗预测生物标志物以及探究免疫治疗的内在机制和耐药机制是取得突破的首要前提。



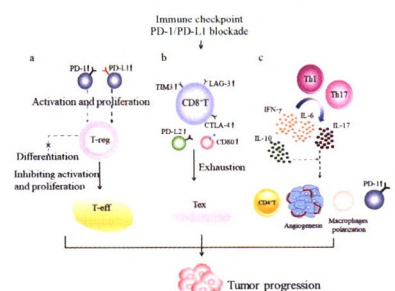
1735

靶向肿瘤 PD-1/PD-L1 抗体药物治疗中出现疾病“超进展”现象及其合理应用研究进展

袁司辰#, 赵慧锋#, 吴昊姝, 曹戟*

(浙江大学药学院, 浙江 杭州 310058)

本文总结近年来在 PD1/PD-L1 单抗治疗肿瘤中出现的肿瘤“超进展”现象, 分析产生该现象的潜在原因及初步机制, 并进一步基于相关生物标志物, 在抗 PD-1/PD-L1 抗体药物合理应用方面做一简单探讨。

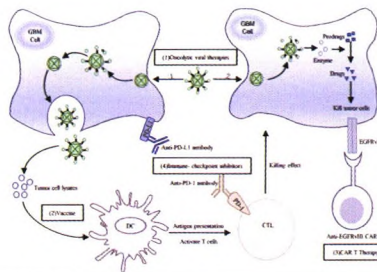


1792

胶质母细胞瘤的免疫治疗研究进展

吕英琪[#], 陈曜星[#], 卫晨萱[#], 江淦^{*}, 高小玲^{*}
(上海交通大学医学院, 上海 200025)

本文主要总结了胶质母细胞瘤的免疫特性、其免疫治疗面临的困难及现有针对胶质母细胞瘤的主要免疫疗法。

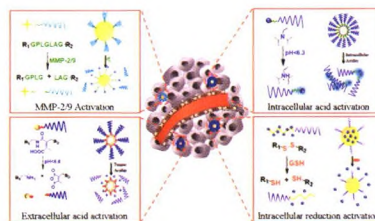


1802

微环境激活型纳米递药系统用于肿瘤免疫治疗的研究进展

侯博^{1,2}, 王当歌¹, 高晶¹, 王晖^{2*}, 李亚平¹, 于海军^{1*}
(1. 中国科学院上海药物研究所, 上海 201203; 2. 内蒙古大学化学化工学院, 内蒙古呼和浩特 010021)

本文围绕本课题组近期研究成果, 详细论述了微环境激活型纳米递药系统实现免疫治疗药物高效递送的化学机制以及该领域的主要挑战和可能发展方向。

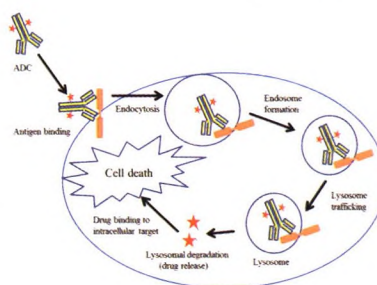


1810

抗体偶联药物发展与进展

宋洪彬^{*}, 刘冬连, 李鹏飞, 赵季冬, 曲妍霏
(东曜药业有限公司, 江苏 苏州 215123)

抗体偶联药物 (antibody-drug conjugates) 将高活性细胞毒药物选择性输送到抗原阳性癌细胞内部, 发挥了抗体特异性靶向优势作用。经过过去几十年的研发, 新一代抗体偶联药物主要由无免疫源性的抗体、稳定的链接子和高活性细胞毒药物组成, 尽管该类药物还存在诸多挑战, 但最近不断临床研究的成功促使抗体偶联药物越来越受到极大关注和兴趣。

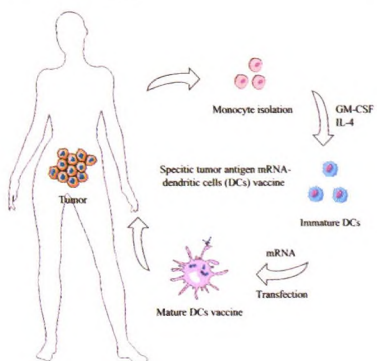


1818

mRNA 致敏的树突状细胞用于肿瘤免疫治疗的研究进展

赵星^{1,2}, 顾杨卓¹, 宋相容^{1*}
(1. 四川大学华西医院生物治疗国家重点实验室, 四川 成都 610041; 2. 贵州医科大学, 组织工程与干细胞实验中心/中国医学科学院成体干细胞转化研究重点实验室, 免疫学教研室, 贵州 贵阳 550004)

mRNA 致敏的 DCs 是一种极具潜力的肿瘤免疫治疗新模式。

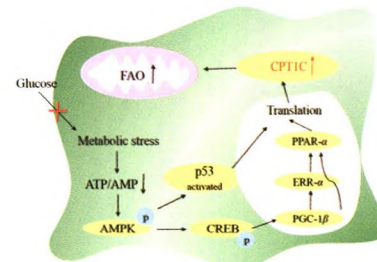


1824

肉毒碱棕榈酰转移酶 1 对肿瘤发生与免疫系统调控研究进展

张明祎, 杜婷婷, 季鸣, 陈晓光^{*}
(中国医学科学院、北京协和医学院药物研究所, 天然药物活性物质与功能国家重点实验室/创新药物非临床药物代谢及 PK/PD 研究北京市重点实验室, 北京 100050)

本文旨在阐述 CPT1 的生物学功能及其不同亚型在肿瘤代谢和免疫调控中的作用, 及其抑制剂的研究进展, 为肿瘤治疗提供新的思路。

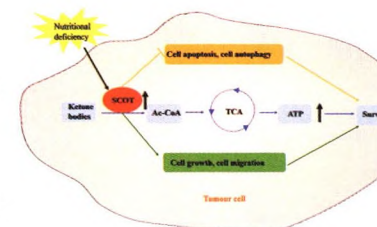


1831

琥珀酰辅酶 A 转移酶 SCOT 在肿瘤代谢中的研究进展

张智慧, 王庆华, 季鸣, 陈晓光^{*}
(中国医学科学院、北京协和医学院药物研究所, 天然药物活性物质与功能国家重点实验室/创新药物非临床药物代谢及 PK/PD 研究北京市重点实验室, 北京 100050)

琥珀酰辅酶 A 转移酶 (SCOT) 在肿瘤细胞中的作用: 肿瘤细胞长期处于的营养缺乏状态可使得 SCOT 高表达, 而 SCOT 可以抑制肿瘤细胞的凋亡和自噬, 促进肿瘤细胞的生长和迁移, 并且通过增强酮体代谢过程, 为细胞提供 ATP, 使得肿瘤细胞得以生存。



研究论文

1837

一种靶向钙结合蛋白 S100A9 重组疫苗的构建及其抗肿瘤活性研究

卢悟广^{1,2}, 曹萌^{1,2}, 桑明^{1,2}, 蔡花漫³, 曹鹏^{1,2*}, 李荣秀^{3*}

(1. 南京中医药大学附属中西医结合医院, 细胞与分子生物学实验室, 江苏 南京 210028; 2. 南京中医药大学药学院, 江苏 南京 210023; 3. 上海交通大学生命科学技术学院, 微生物代谢国家重点实验室, 上海 200240)

CTB-S100A9 疫苗能够抑制肿瘤诱导的 MDSC 和 Treg, 从而抑制肿瘤的生长和转移。



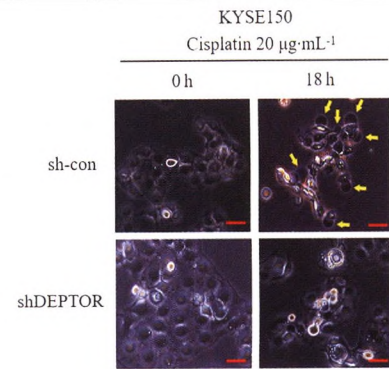
1845

DEPTOR 诱导 Caspase-1 介导的细胞焦亡提高食管鳞癌细胞顺铂化疗敏感性

段晶晶¹, 徐慧欣¹, 骆璞¹, 潘文俊¹, 董晓颖², 郑航^{1*}

(南方医科大学南方医院 1. 肿瘤科, 2. 胸外科, 广东 广州 510515)

DEPTOR 可以通过增加 Caspase-1 介导的细胞焦亡, 提高食管鳞癌细胞对顺铂化疗敏感性。



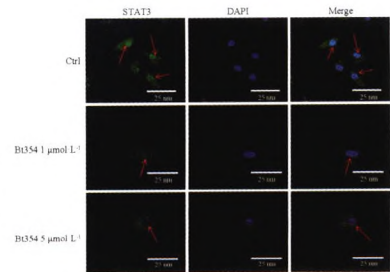
1851

STAT3 靶点抑制剂 Bt354 抗前列腺癌作用及其分子机制研究

王雨辰, 陈越, 季鸣, 薛妮娜, 陈晓光*

(中国医学科学院、北京协和医学院药物研究所, 天然药物活性物质与功能国家重点实验室/创新药物非临床药物代谢及 PK/PD 研究北京市重点实验室, 北京 100050)

本文主要研究了 STAT3 靶点抑制剂 Bt354 抗前列腺癌的药效学研究, 并初步解释了其作用机制。研究结果提示, Bt354 可能是一种对 STAT3 激活的前列腺癌细胞有效的抗癌剂。



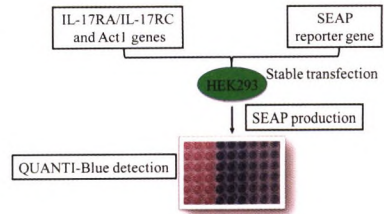
1858

IL-17 信号通路抑制剂细胞筛选模型的优化及应用

薛妮娜, 季鸣, 张明祎, 刘羿晨, 陈晓光*

(中国医学科学院、北京协和医学院药物研究所, 天然药物活性物质与功能国家重点实验室/创新药物非临床药物代谢及 PK/PD 研究北京市重点实验室, 北京 100050)

HEK-Blue IL-17 细胞模型稳定表达人源 IL-17RA/IL-17RC 异二聚体受体和 Act1 衔接分子, 同时还表达 SEAP 报告基因。通过 QUANTI-Blue 检测 SEAP 的生成量, 从而反映 IL-17A 和 IL-17F 介导的信号通路活化状态。建立并优化该细胞模型, 用于筛选 IL-17 信号通路抑制剂。



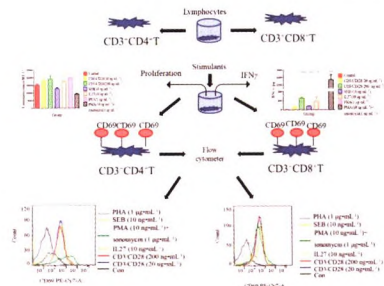
1863

不同刺激剂对人淋巴细胞活化的影响

闫征, 薛妮娜, 季鸣, 来芳芳, 陈晓光*

(中国医学科学院、北京协和医学院药物研究所, 天然药物活性物质与功能国家重点实验室/创新药物非临床药物代谢及 PK/PD 研究北京市重点实验室, 北京 100050)

CD3/CD28 抗体、PMA+ionomycin、SEB 和 IL27 作用 PBMC 24 h 不影响淋巴细胞增殖, 但可以很好地活化 CD3⁺CD4⁺和 CD3⁺CD8⁺ T 细胞, 表现为 CD69 的平均荧光强度显著右移, 并促进淋巴细胞 IFN-γ 的分泌。CD3/CD28 抗体、PMA+ionomycin、SEB 和 IL27 是 T 细胞活化的有效刺激剂。



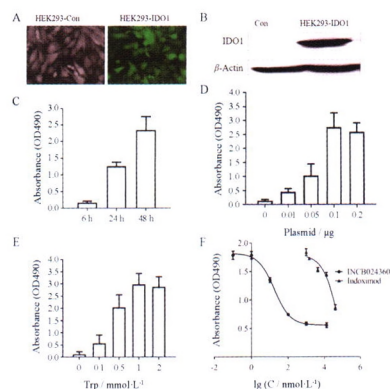
1868

基于酶学-细胞水平的 IDO1 抑制剂筛选模型建立与优化

来芳芳, 薛妮娜, 季鸣, 杜婷婷, 李凌, 盛莉, 陈晓光*

(中国医学科学院、北京协和医学院药物研究所, 天然药物活性物质与功能国家重点实验室/创新药物非临床药物代谢及 PK/PD 研究北京市重点实验室, 北京 100050)

本研究以肿瘤免疫治疗相关蛋白吲哚胺 2,3-双加氧酶 1 (indoleamine 2,3-dioxygenase 1, IDO1) 为靶点, 设计构建了基于酶学-细胞水平的 IDO1 抑制剂筛选模型并进行了动物体内验证。



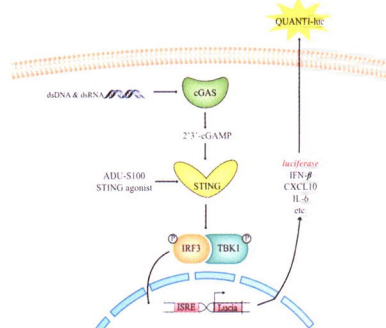
1875

STING 激动剂细胞筛选模型的建立和应用

王明晋, 伏蓉, 姜慧敏, 金晶*, 陈晓光*

(中国医学科学院、北京协和医学院药物研究所, 天然药物活性物质与功能国家重点实验室/创新药物非临床药物代谢及 PK/PD 研究北京市重点实验室, 北京 100050)

本研究基于 THP-1-Dual 细胞和 THP-1 KO-STING 细胞, 建立了可以通过荧光素酶检测的 STING 激动剂筛选方法。



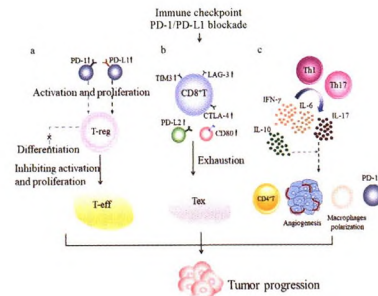
信息

《药学报》英文刊 2019 年第 5 期图文摘要

1735

Advances in hyperprogressive disease of PD-1/PD-L1 antibody drugs and rational drug therapyYUAN Si-chen[#], ZHAO Hui-feng[#], WU Hao-shu, CAO Ji^{*}*(College of Pharmaceutical Sciences, Zhejiang University, Hangzhou 310058, China)*

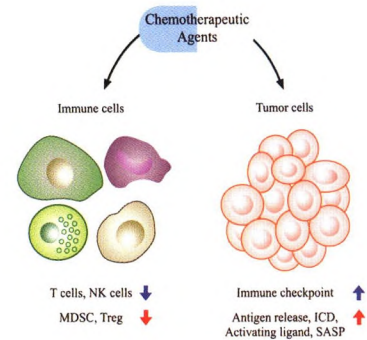
In this review, we summarize the progress and potential reasons of hyperprogressive disease caused by PD-1/PD-L1 blockade, and further discuss its application based on the rational use of biomarkers for searching the benefit patients.



1741

Mechanistic advancement in chemotherapeutic agents modulated antitumor immune responseXU Jun^{1,2}, GENG Mei-yu^{1,2}, HUANG Min^{1,2*}*(1. State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, China; 2. University of Chinese Academy of Sciences, Beijing 100009, China)*

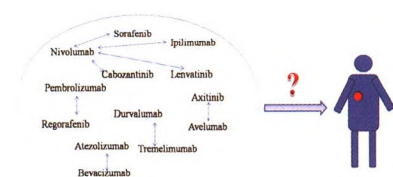
While killing tumor cells through cytotoxicity effect, chemotherapeutic agents also have complex effects on tumor immune microenvironment. Chemotherapeutic agents can inhibit the proliferation and function of immune cells and can also reshape the immunogenicity of tumor cells through various mechanisms, thereby changing the immune microenvironment of tumors and producing immune-mediated antitumor effect.



1749

Review on clinical research progress of immunotherapy in liver cancerYAN Shi-jia, LIU Xian-ya, WAN Guo-hui^{*}*(School of Pharmaceutical Sciences, Sun Yat-san University, Guangzhou 510006, China)*

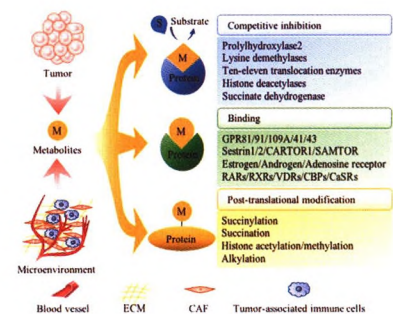
At present, clinical trials combining immune checkpoint inhibitors and tyrosine kinase inhibitors are undergoing, expecting to bring new breakthroughs in the treatment of advanced hepatocellular carcinoma.



1755

Mechanisms of metabolite-triggered oncogenic signaling in cancerWANG Xiao-min^{1,2}, HUANG Min^{1,2*}*(1. State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, China; 2. University of Chinese Academy of Sciences, Beijing 100009, China)*

Metabolic remodeling in cancer often results in the intracellular accumulation of particular metabolites. Some of these metabolites, particularly those well-defined onco-metabolites, may exhibit metabolism-independent roles as signaling molecules, which may trigger oncogenic signaling *via* various mechanisms including competitive inhibition, protein post-translational modifications and direct protein binding, and in turn promote cancer malignancy.



1771

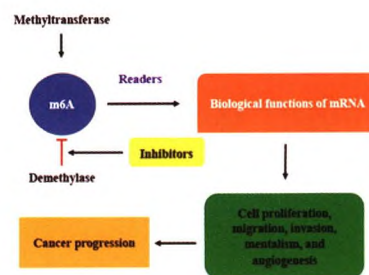
The roles of m⁶A in cancer biology and its targeted therapy

PENG Yan-xi, DU Jun, WANG Hong-sheng*

(School of Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou 510006, China)

The present review summarizes biological functions of m⁶A on splicing, nuclear export, translation, and degradation of mRNA. m⁶A regulates the cellular functions including proliferation, migration, invasion, metastasis, and angiogenesis. As to the *in vivo* functions, m⁶A can modulate the progression of various cancers including acute myelocytic leukemia, breast, liver and colorectal cancer.

Nowadays, the inhibitors of m⁶A related enzymes including FTO and ALKBH5 are being developed. We further discussed the potential therapeutic values of m⁶A and its related proteins on cancer therapy and treatment.



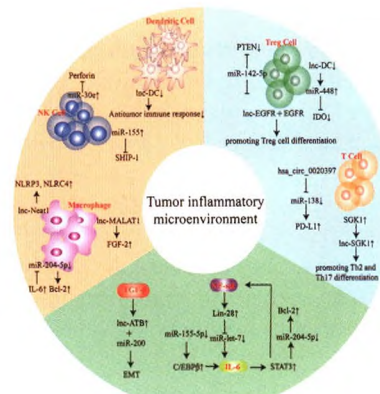
1783

Non-coding RNA and tumor immune regulation

GUO Qiao-ru¹, LIU Yun¹, SU Chao-yue¹, WANG Hui², ZHANG Jian-ye^{1*}

(1. Guangdong Provincial Key Laboratory of Molecular Target and Clinical Pharmacology, School of Pharmaceutical Sciences, Guangzhou Medical University, Guangzhou 511436, China; 2. Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangzhou 510623, China)

Non-coding RNA (ncRNA) plays a vital role in the initiation and development of tumor, the immune system also exhibits more complex function in tumor development. As an important means of tumor therapy, tumor immunotherapy can be regulated by non-coding RNA to achieve the goal of treatment. This article summarizes the regulation of tumor immunity by non-coding RNA.



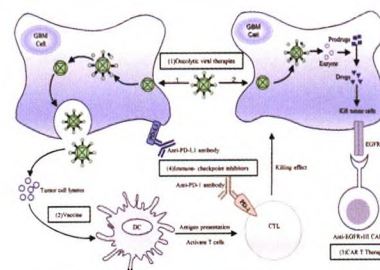
1792

Research progress in immunotherapy for glioblastoma

LÜ Ying-qi[#], CHEN Yao-xing[#], WEI Chen-xuan[#], JIANG Gan*, GAO Xiao-ling*

(School of Medicine, Shanghai Jiao Tong University, Shanghai 200025, China)

This review summarizes the immunological characteristics of glioblastoma (GBM), points out the difficulties for GBM immunotherapy, and overviews the current immunotherapies against GBM.



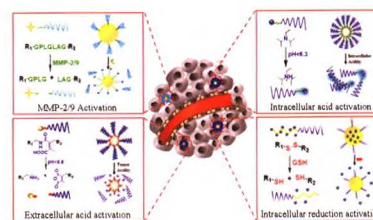
1802

Advances of microenvironment-activated nanosized drug delivery system for cancer immunotherapy

HOU Bo^{1,2}, WANG Dang-ge¹, GAO Jing¹, WANG Hui^{2*}, LI Ya-ping¹, YU Hai-jun^{1*}

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This paper summarized the recent progress of our research group about the microenvironment-activated nanosized drug delivery system (NDDS) for efficient delivery of immunotherapeutic, and briefly discussed the challenges and perspective of NDDS-based cancer immunotherapy.



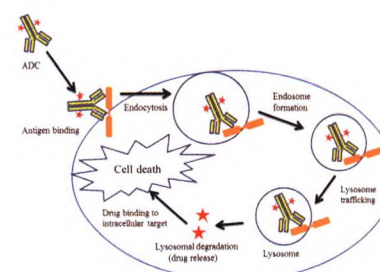
1810

Advanced research and technology development of antibody-drug conjugates

SONG Hong-bin*, LIU Dong-lian, LI Peng-fei, ZHAO Ji-dong, QU Yan-fei

(TOT Biopharm, Suzhou 215123, China)

Antibody-drug conjugates (ADCs) aim to take advantage of the specificity of monoclonal antibodies (mAbs) to deliver potent cytotoxic drugs selectively to antigen-expressing tumor cells. Advancements over the past several decades have led to a new generation of ADCs comprising non-immunogenic mAbs, linkers with balanced stability and highly potent cytotoxic agents. Although challenges remain, recent clinical success has generated intense interest in this therapeutic class.



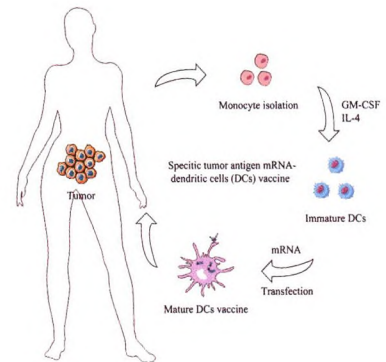
1818

Research progress of dendritic cells anti-tumor vaccine stimulated by mRNA

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Pulsing DCs with mRNAs is a new and highly promising modality in cancer immunotherapy.



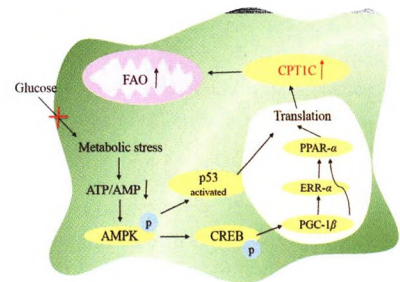
1824

Research progress of carnitine palmitoyltransferase 1 in tumor immunotherapy

ZHANG Ming-yi, DU Ting-ting, JI Ming, CHEN Xiao-guang*

(State Key Laboratory of Bioactive Substances and Functions of Natural Medicines/Beijing Key Laboratory of Non-clinical Drug Metabolism and PK/PD Study, Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100050, China)

This article aims to review the biological functions of CPT1 and the role of different subtypes in tumor metabolism and immune regulation, and the research progress of its inhibitors, providing new ideas for cancer treatment.



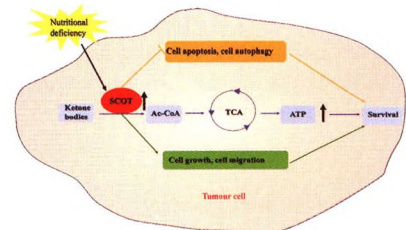
1831

Research advancement of succinyl-CoA transferase SCOT in tumor metabolism

ZHANG Zhi-hui, WANG Qing-hua, JI Ming, CHEN Xiao-guang*

(State Key Laboratory of Bioactive Substances and Functions of Natural Medicines/Beijing Key Laboratory of Non-clinical Drug Metabolism and PK/PD Study, Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100050, China)

The role of succinyl-CoA transferase (SCOT) in tumor cells: The long-term lack of nutrient status of tumor cells can make SCOT high expression, while SCOT can inhibit tumor cell apoptosis and autophagy, promote tumor cell growth and migration, and provide ATP to the cells by enhancing ketone bodies metabolism, which allows tumor cells to survive.



Original Articles

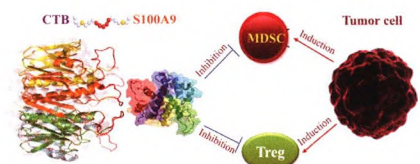
1837

Construction and anti-tumor efficacy of a peptide vaccine that targets calcium-binding protein S100A9

LU Wu-guang^{1,2}, CAO Meng^{1,2}, SANG Ming^{1,2}, CAI Hua-man³, CAO Peng^{1,2*}, LI Rong-xiu^{3*}

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CTB-S100A9 vaccination inhibit tumor induced MDSC and Treg, thereby suppress tumor growth and metastasis.



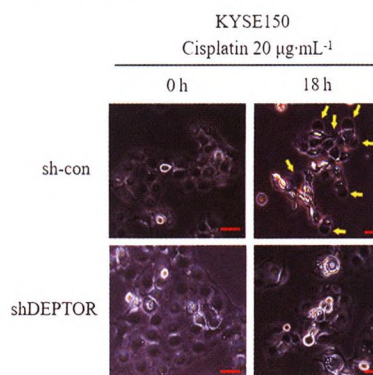
1845

DEPTOR improves cisplatin chemosensitivity in esophageal squamous cell carcinoma cells by inducing Caspase-1-mediated pyroptosis

DUAN Jing-jing¹, XU Hui-xin¹, LUO Pu¹, PAN Wen-jun¹, DONG Xiao-ying², ZHENG Hang¹*

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DEPTOR can improve cisplatin chemosensitivity in ESCC cells via inducing Caspase-1-mediated pyroptosis.



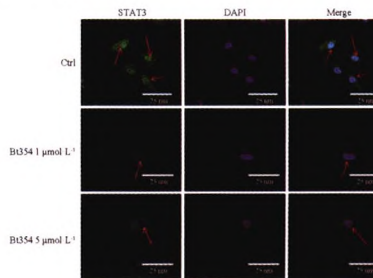
1851

The antitumor activity of STAT3 target inhibitor Bt354 and molecular mechanism of anti-prostate cancer

WANG Yu-chen, CHEN Yue, JI Ming, XUE Ni-na, CHEN Xiao-guang*

(State Key Laboratory of Bioactive Substances and Functions of Natural Medicines/Beijing Key Laboratory of Non-clinical Drug Metabolism and PK/PD Study, Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100050, China)

In this study, we investigated that the performance of our previous reported STAT3 inhibitor Bt354 as a potent anticancer agent for STAT3 activated prostate cancer cells.



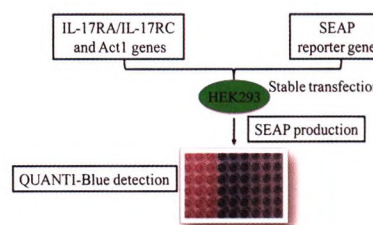
1858

The optimization and application of cell-based screening model for IL-17-mediated signaling pathway

XUE Ni-na, JI Ming, ZHANG Ming-yi, LIU Yi-chen, CHEN Xiao-guang*

(State Key Laboratory of Bioactive Substances and Functions of Natural Medicines/Beijing Key Laboratory of Non-clinical Drug Metabolism and PK/PD Study, Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100050, China)

HEK-Blue IL-17 cells are stably transfected with the IL-17RA/RC heterodimer, the Act1 adaptor molecule and SEAP receptor gene. The SEAP secretion detected by QUANTI-Blue solution is in response to the activation of the IL-17A and IL-17F-mediated signaling pathway. The optimization and application of HEK-Blue IL-17 cells model is to screen the targeted IL-17 signaling drugs.



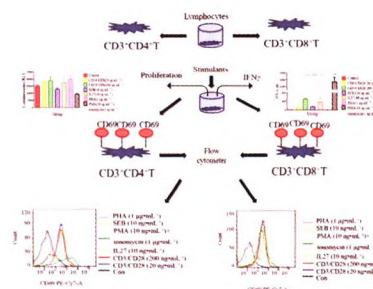
1863

The effects of different stimulators on the activation of human lymphocytes

YAN Zheng, XUE Ni-na, JI Ming, LAI Fang-fang, CHEN Xiao-guang*

(State Key Laboratory of Bioactive Substances and Functions of Natural Medicines/Beijing Key Laboratory of Non-clinical Drug Metabolism and PK/PD Study, Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100050, China)

The proliferation of lymphocytes had no change after exposed of CD3/CD28 antibody, SEB, IL27 and PMA plus ionomycin for 24 h. However, the CD69 expressions in CD3⁺CD4⁺ and CD3⁺CD8⁺ T cells and IFN γ productions were significantly increased by CD3/CD28 antibody, SEB, IL27 and PMA plus ionomycin at 24 h, indicating that CD3⁺CD4⁺ and CD3⁺CD8⁺ T cells were activated under above-mentioned stimulated condition. CD3/CD28 antibody, SEB, IL27 and PMA plus ionomycin were valid stimulators for T cell activation.



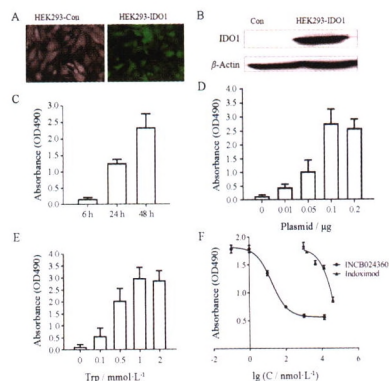
1868

Establishment and optimization of an enzyme-cell based high-throughput screening platform for IDO1 inhibitors

LAI Fang-fang, XUE Ni-na, JI Ming, DU Ting-ting, LI Ling, SHENG Li, CHEN Xiao-guang*

(State Key Laboratory of Bioactive Substances and Functions of Natural Medicines/Beijing Key Laboratory of Non-clinical Drug Metabolism and PK/PD Study, Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100050, China)

In this study, we used the tumor immunotherapy protein indoleamine 2,3-dioxygenase 1 (IDO1) as the target, and proposed an enzyme-cell-based tertiary IDO1 inhibitor high throughput screening platform. Further, we verified the inhibitory activity of the IDO1 inhibitor *in vivo*.



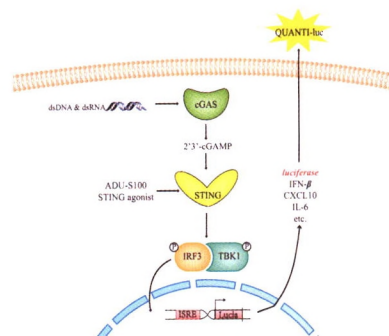
1875

Establishment and application of STING agonist *in-vitro* screening model

WANG Ming-jin, FU Rong, JIANG Hui-min, JIN Jing*, CHEN Xiao-guang*

(State Key Laboratory of Bioactive Substances and Functions of Natural Medicines/Beijing Key Laboratory of Non-clinical Drug Metabolism and PK/PD Study, Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100050, China)

In this study, based on THP-1-Dual cells and THP-1 KO-STING cells, a screening method for STING agonists was established by detection of luciferase.



ACTA PHARMACEUTICA SINICA

Volume 54 Number 10 2019 October



期刊基本参数: CN 11-2163/R*1953*m*A4*170*zh*P* ¥40.00* *22*2019-10

本期责任编辑 王 燕

药学报 (YAOXUE XUEBAO)

(月刊, 1953年7月创刊)

主管单位: 中国科学技术协会

主办单位: 中国药学会 (<http://www.cpa.org.cn>)

中国医学科学院药物研究所
(<http://www.imm.ac.cn>)

编辑出版: 药学报编辑部 (100050 北京市先农坛街1号)

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主编: 王晓良

印刷: 北京科信印刷有限公司

国内订购: 全国各地邮电局

发行范围: 公开发行人

国内: 北京报刊发行局

国外: 中国国际图书贸易集团有限公司
(北京市399信箱, 100044)

ACTA PHARMACEUTICA SINICA

(Monthly, Founded in 1953 July)

Directed by: China Association for Science and Technology

Sponsored by: Chinese Pharmaceutical Association

(<http://www.cpa.org.cn>)

Institute of Materia Medica, Chinese Academy of Medical
Sciences (<http://www.imm.ac.cn>)

Edited and Published by: Editorial Office of Acta Pharmaceutica Sinica

(1 Xiannongtan Street, Beijing 100050).

Tel / Fax: 86-10-63026192, 63035012;

E-mail: yxxb@imm.ac.cn; <http://www.yxxb.com.cn>

Editor-in-chief: WANG Xiao-liang

Printed by: Beijing Kexin Printing Co., Ltd.

Domestic subscriptions: Local Post Offices

Distribution

Domestic: Beijing Post Offices

Foreign: China International Book Trading Corporation,
PO Box 399, Beijing 100044, China

ISSN 0513-4870

CN 11-2163/R

2019年 第54卷 第10期

2019, Vol. 54, No.10

2019年10月12日出版

Publication Date: 2019-10-12

邮发代号: 2-233

Code number: M105

国内定价: 每期40.00元



万方数据

ISSN 0513-4870



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