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Hematopoietic Transcription Factor RUNX1 is Essential for Promoting Macrophage–Myofibroblast Transition in Non-Small-Cell Lung Carcinoma

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Macrophage-myofibroblast transition (MMT) is a newly discovered pathway for mass production of pro-tumoral cancer-associated fibroblasts (CAFs) in non-small cell lung carcinoma (NSCLC) in a TGF-β1/Smad3 dependent manner. Better understanding its regulatory signaling in tumor microenvironment (TME) may identify druggable target for the development of precision medicine. Here, by dissecting the transcriptome dynamics of tumor-associated macrophage at single-cell resolution, a crucial role of a hematopoietic transcription factor Runx1 in MMT formation is revealed. Surprisingly, integrative bioinformatic analysis uncovers Runx1 as a key regulator in the downstream of MMT-specific TGF-β1/Smad3 signaling. Stromal Runx1 level positively correlates with the MMT-derived CAF abundance and mortality in NSCLC patients. Mechanistically, macrophage-specific Runx1 promotes the transcription of genes related to CAF signatures in MMT cells at genomic level. Importantly, macrophage-specific genetic deletion and systemic pharmacological inhibition of TGF-β1/Smad3/Runx1 signaling effectively prevent MMT-driven CAF and tumor formation in vitro and in vivo, representing a potential therapeutic target for clinical NSCLC.

1. Introduction

Lung carcinoma is a major cause of death worldwide. There were 5422 new cases of lung cancer in 2020 and ranked as the top cause of cancer deaths in 2020 in Hong Kong (Hong Kong Cancer Registry). Surgery, chemotherapy, and radiotherapy have been the mainstays of treatment for decades. However, outcomes are still unsatisfactory due to side effects, metastasis, and drug resistance.[1] Cancer cells are heterogeneous, versatile, and adaptable, leading to primary and secondary resistance.[2] Therapies that target tumor microenvironment (TME) show promise as cancer growth, invasion, and metastasis rely on stromal conditions.[3] Unexpectedly, only less than 30% of non-small-cell lung carcinoma (NSCLC) patients respond to the latest programmed cell death protein-1 receptor (PD-1) and PD-ligand-1 (PD-L1) targeted therapy.[4] Better understanding the

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Acknowledgements
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The ORCID identification number(s) for the author(s) of this article can be found under https://doi.org/10.1002/advs.202302203

DOI: 10.1002/advs.202302203

Cancer Letters 550 (2022) 215925

Contents lists available at ScienceDirect

Cancer Letters

journal homepage: www.elsevier.com/locate/canlet

TGF-β signaling networks in the tumor microenvironment

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ARTICLE INFO

Keywords:
TGF-β signaling
Tumor microenvironment
Immunity
Cancer
Targeted therapy

ABSTRACT

Transforming growth factor-β (TGF-β) signaling shows important roles in both physiology and pathology, especially in the progression of inflammatory diseases including cancer. Interestingly, TGF-β was first reported as a cancer suppressor, but increasing evidence confirmed its protumoral actions. Paradoxically, TGF-β can be produced by both cancer cells and stromal cells as a signaling network, which actively shapes the tumor microenvironment (TME). Surprisingly, disruption of TGF-β signaling results in both anti-cancer and pro-tumoral phenotypes in experimental cancer models, revealing the unexpected complexity of its downstream pathways for mediating cancer progression. Thus, a better understanding of the underlying mechanisms of TGF-β signaling at the molecular level can bring new insights for developing medications that can precisely separate the anti-cancer actions from the tumor-promoting outcomes. Here, we systematically summarized the latest discoveries of TGF-β signaling in cancer cells and the TME and discussed their translational implications for cancer.

1. Introduction

Transforming growth factor-β (TGF-β) signaling has pleiotropic roles in both normal physiology and pathology, including cell proliferation, differentiation, and tissue fibrosis [1–3]. It can be activated by a superfamily of cytokines, e.g TGF-β, activin, inhibin, and bone morphogenetic protein (BMP) etc, where TGF-β1 is almost ubiquitously expressed in mammalian tissues [4]. TGF-β signaling can execute its cellular responses in a Smad-dependent manner via canonical pathway [5], or non-canonical pathway via Smad-independent mechanisms e.g. mitogen-activated protein kinase (MAPK) pathways and the TRAF6/-phosphatidylinositol 3′-kinase (PI3K)/protein kinase B (Akt) cascade [6].

Increasing evidence demonstrated the importance of TGF-β signaling in cancer. Interestingly, it is not only reported as a cancer suppressor during carcinogenesis [7], but also a tumor promoter in the cancer progression [8]. Unexpectedly, either cancer or stromal cells derived TGF-β show regulatory roles in both cancer cells and tumor microenvironment (TME) [9,10]. Importantly, genetic and pharmaceutical disruption of TGF-β signaling results in both anticancer and protumoral effects in experimental cancer models [11,12], highlighting its importance and complexity in cancer development and progression.

A better understanding of the underlying mechanisms of TGF-β signaling in cancer as well as the TME can help to identify new diagnostic markers and therapeutic targets for cancer [13], evidencing the rapid growth of related studies these years. In this review, we collected the new insights into TGF-β signaling in cancer cells and TME for regulating the cancer progression, and systematically summarized and discussed their therapeutic implications for precision medicine against cancer.

2. TGF-β signaling in cancer cells

TGF-β plays a vital role in cancer development. It not only can act as

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https://doi.org/10.1016/j.canlet.2022.215925
Received 27 April 2022; Received in revised form 5 September 2022; Accepted 17 September 2022
Available online 29 September 2022

nature communications

Article

https://doi.org/10.1038/s41467-023-37515-8

Smad3 is essential for polarization of tumor-associated neutrophils in non-small cell lung carcinoma

Received: 5 October 2020

Accepted: 20 March 2023

Published online: 3 March 2023

Check for updates

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Neutrophils are dynamic with their phenotype and function shaped by the microenvironment, such as the N1 antitumor and N2 pro-tumor states within the tumor microenvironment (TME), but its regulation remains undefined. Here we examine TGF-β1/Smad3 signaling in tumor-associated neutrophils (TANs) in non-small cell lung carcinoma (NSCLC) patients. Smad3 activation in N2 TANs is negatively correlate with the N1 population and patient survival. In experimental lung carcinoma, TANs switch from a predominant N2 state in wild-type mice to an N1 state in Smad3-KO mice which associate with enhanced neutrophil infiltration and tumor regression. Neutrophil depletion abrogates the N1 anticancer phenotype in Smad3-KO mice, while adoptive transfer of Smad3-KO neutrophils reproduces this protective effect in wild-type mice. Single-cell analysis uncovers a TAN subset showing a mature N1 phenotype in Smad3-KO TME, whereas wild-type TANs mainly retain an immature N2 state due to Smad3. Mechanistically, TME-induced Smad3 target genes related to cell fate determination to preserve the N2 state of TAN. Importantly, genetic deletion and pharmaceutical inhibition of Smad3 enhance the anticancer capacity of neutrophils against NSCLC via promoting their N1 maturation. Thus, our work suggests that Smad3 signaling in neutrophils may represent a therapeutic target for cancer immunotherapy.

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IMMUNOLOGY

Single-cell RNA sequencing uncovers a neuron-like macrophage subset associated with cancer pain

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Tumor innervation is a common phenomenon with unknown mechanism. Here, we discovered a direct mechanism of tumor-associated macrophage (TAM) for promoting de novo neurogenesis via a subset showing neuronal phenotypes and pain receptor expression associated with cancer-driven nocifensive behaviors. This subset is rich in lung adenocarcinoma associated with poorer prognosis. By elucidating the transcriptome dynamics of TAM with single-cell resolution, we discovered the novel phenomenon "macrophage to neuron-like cell transition" (MNT) for directly promoting tumoral neurogenesis, evidenced by macrophage depletion and fate-mapping study in lung carcinoma models. Encouragingly, we detected neuronal phenotypes and activities of the bone marrow–derived macrophage MNT cells (MNTs) in vitro. Adoptive transfer of MNTs into NOD/SCID mice markedly enhanced their cancer-associated nocifensive behaviors. We identified macrophage-specific Smad3 as a pivotal regulator for promoting MNT at the genomic level; its disruption effectively blocked the tumor innervation and cancer-dependent nocifensive behaviors in vivo. Thus, MNT may represent a novel therapeutic target for cancer pain.

INTRODUCTION

Cancer is still a leading cause of death worldwide. Ineffective treatments, severe side effects, drug resistance, recurrence, and metastasis are the major barriers to cancer symptom management and cure (*1*). In particular, about half of all patients diagnosed with malignancies experience chronic pain, which seriously affects their quality of life. This is especially pertinent in patients with advanced cancers of the lung, breast, prostate, or gastrointestinal tract, as two-thirds of these patients suffer from chronic pain (*2*, *3*). Globally, nearly 80% of cancer patients, including pediatric patients, have inadequate pain control (*4*). It is therefore of paramount importance to elucidate the underlying mechanisms of cancer pain to guide therapeutics development.

Cancer pain is thought to be partly caused by tissue damage and inflammation in the tumor microenvironment (TME) via unclear mechanisms (*4*). Clinically, chronic inflammation is often associated with the development and progression of cancer (*5*, *6*). It is still unclear how chronic inflammation drives cancer complications especially chronic pain (*4*). In the past few decades, neuronal plasticity has been established as a key mechanism for the development and maintenance of chronic pain (*7*, *8*). Peripheral sensitization commonly occurs after peripheral tissue injury and inflammation at the nociceptor level; it is essential for transiting acute nociception into chronic pain (*9*, *10*). Nociceptive sensory neurons not only respond to immune signals but also directly modulate inflammation, evidenced by the finding that silencing nociceptor reduces inflammation in the allergic airway (*11*).

Increasing evidence suggests that numerous non-neuronal cell types play an important role in pain sensation including cancer cells and macrophages (*4*). An emerging role for macrophages in periphery pain regulation has recently been suggested. Accordingly, depletion of macrophages, but not of neutrophils or T cells, significantly attenuates the development of incision and pathogen-induced mechanical and thermal hypersensitivity in mice (*12*). This is accompanied by the down-regulation of interleukin-1β (IL-1β) and other pro-algetic mediators at inflammatory sites (*13*). Macrophages were also found to affect analgesia by indirectly releasing anti-inflammatory mediators, such as IL-10 and specialized pro-resolution mediators (*14*, *15*). Furthermore, a recent study demonstrated that resident microglia and peripheral monocytes act synergistically to initiate hypersensitivity and promote chronic pain after peripheral nerve injury (*16*). Although the involvement of macrophages in evoked pain has been suggested by the suppressive effect of macrophage depletion on mechanical and cold hypersensitivity (*17*, *18*), the functional role and regulatory mechanism of macrophages, especially tumor-associated macrophages (TAMs), in cancer pain is still largely unknown.

Single-cell RNA sequencing (scRNA-seq) is an emerging approach to resolve cellular heterogeneity on a genome-wide scale. It

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IVYSPRING INTERNATIONAL PUBLISHER

International Journal of Biological Sciences

2022; 18(14): 5489-5502. doi: 10.7150/ijbs.72977

Research Paper

AANG Prevents Smad3-dependent Diabetic Nephropathy by Restoring Pancreatic β-Cell Development in db/db Mice

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Received: 2022.03.17; Accepted: 2022.05.29; Published: 2022.08.29

Abstract

Diabetic nephropathy (DN) is a major cause of end-stage kidney disease, where TGF-β1/Smad signaling plays an important role in the disease progression. Our previous studies demonstrated a combination of Traditional Chinese Medicine derived Smad7 agonist Asiatic Acid (AA) and Smad3 inhibitor Naringenin (NG), AANG, effectively suppressed the progression of renal fibrosis *in vivo*. However, its implication in type-2 diabetic nephropathy (T2DN) is still unexplored. Here, we detected progressive activation of Smad3 but reduction of Smad7 in db/db mice during T2DN development. Therefore, we optimized the dosage and the combination ratio of AANG to achieve a better rebalancing Smad3/Smad7 signaling for treatment of T2DN. Unexpectedly, preventive treatment with combined AANG from week 4 before the development of diabetes and T2DN effectively protected against the onset of T2DN. In contract, these inhibitory effects were lost when db/db mice received the late AANG treatment from 12-24 weeks. Surprisingly, preventive treatment with AANG ameliorated not only T2DN but also the primary disease type-2 diabetes (T2D) with relative normal levels of fasting blood glucose and HbA1c, and largely improving metabolic abnormalities especially on insulin insensitivity and glucose tolerance in db/db mice. Mechanistically, AANG effectively prevented both Smad3-mediated renal fibrosis and NF-κB-driven renal inflammation in the diabetic kidney *in vivo* and advanced glycation end-products (AGE) stimulated tubular epithelial mTEC cells *in vitro*. More importantly, we uncovered that preventive treatment with AANG effectively protected against diabetic-associated islet injury via restoring the β cell development in db/db mice. Taken together, we discovered that the early treatment with combined AANG can effectively protect against the development of T2D and T2DN via mechanism associated with protection against Smad3-depenedent islet injury.

Key words: Type-2 diabetes, Asiatic Acid, Naringenin, Islet, Nephropathy

Introduction

Diabetes mellitus affects 346 million people worldwide and 582.5 thousand Hong Kong population with 10-20% mortality due to kidney failure (International Diabetes Federation 2015, Centers for Disease Control and Prevention 2011). Its onset and progression are multifactorial but largely due to the development of systemic insulin resistance and insufficient insulin secretion [1-3]. Although a

non-coding RNA

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Review

LncRNA-Dependent Mechanisms of Transforming Growth Factor-β: From Tissue Fibrosis to Cancer Progression

Philip Chiu-Tsun Tang [1,†], Ying-Ying Zhang [2,†], Jane Siu-Fan Li [1,†], Max Kam-Kwan Chan [1], Jiaoyi Chen [3], Ying Tang [4], Yiming Zhou [5], Dongmei Zhang [6], Kam-Tong Leung [7], Ka-Fai To [1], Sydney Chi-Wai Tang [3], Hui-Yao Lan [8] and Patrick Ming-Kuen Tang [1,*]

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Abstract: Transforming growth factor-β (TGF-β) is a crucial pathogenic mediator of inflammatory diseases. In tissue fibrosis, TGF-β regulates the pathogenic activity of infiltrated immunocytes and promotes extracellular matrix production via de novo myofibroblast generation and kidney cell activation. In cancer, TGF-β promotes cancer invasion and metastasis by enhancing the stemness and epithelial mesenchymal transition of cancer cells. However, TGF-β is highly pleiotropic in both tissue fibrosis and cancers, and thus, direct targeting of TGF-β may also block its protective anti-inflammatory and tumor-suppressive effects, resulting in undesirable outcomes. Increasing evidence suggests the involvement of long non-coding RNAs (lncRNAs) in TGF-β-driven tissue fibrosis and cancer progression with a high cell-type and disease specificity, serving as an ideal target for therapeutic development. In this review, the mechanism and translational potential of TGF-β-associated lncRNAs in tissue fibrosis and cancer will be discussed.

Keywords: long non-coding RNA; fibrosis; transforming growth factor-β; cancer; Smad3; TGF-β

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Citation: Tang, P.C.-T.; Zhang, Y.-Y.; Li, J.S.-F.; Chan, M.K.-K.; Chen, J.; Tang, Y.; Zhou, Y.; Zhang, D.; Leung, K.-T.; To, K.-F.; et al. LncRNA-Dependent Mechanisms of Transforming Growth Factor-β: From Tissue Fibrosis to Cancer Progression. *Non-Coding RNA* **2022**, *8*, 36. https://doi.org/10.3390/ncrna8030036

Academic Editor: George A Calin

Received: 22 April 2022
Accepted: 21 May 2022
Published: 25 May 2022

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

1. Introduction

Long non-coding RNAs (lncRNAs) are transcripts with lengths of over 200 nucleotides that together with short microRNAs (miRNAs), small interfering RNAs (siRNAs), small nucleolar RNAs (snoRNAs), small nuclear RNAs (snRNAs), and PIWI-interacting RNAs (piRNAs) constitute a spectrum of non-coding RNA molecules (ncRNAs) characterized by their gene-regulating functions [1–3]. Of these, lncRNAs and miRNAs are two major classes of ncRNAs that participate in the pathogenesis of cancer and fibrotic diseases, as dysregulation of lncRNAs and miRNAs interferes with the control of crucial biological processes, including cell proliferation, apoptosis, and extracellular matrix homeostasis [4,5].

Received: 30 June 2021 | Revised: 27 August 2021 | Accepted: 1 September 2021

DOI: 10.1111/jcmm.16928

ORIGINAL ARTICLE

WILEY

AANG: A natural compound formula for overcoming multidrug resistance via synergistic rebalancing the TGF-β/Smad signalling in hepatocellular carcinoma

Jeff Yat-Fai Chung[1] | Max Kam-Kwan Chan[1] | Philip Chiu-Tsun Tang[1] | Alex Siu-Wing Chan[2] | Justin Shing-Yin Chung[1] | Xiao-Ming Meng[3] | Ka-Fai To[1] | Hui-Yao Lan[4] | Kam-Tong Leung[5] | Patrick Ming-Kuen Tang[1]

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Funding information

The Chinese University of Hong Kong's Faculty Innovation Award, Grant/Award Number: 4620528; Research Grants Council of Hong Kong, Grant/Award Number: 14106518, 14111019 and 14111720

Abstract

Cancer cells are high in heterogeneity and versatility, which can easily adapt to the external stresses via both primary and secondary resistance. Targeting of tumour microenvironment (TME) is a new approach and an ideal therapeutic strategy especially for the multidrug resistant cancer. Recently, we invented AANG, a natural compound formula containing traditional Chinese medicine (TCM) derived Smad3 inhibitor Naringenin (NG) and Smad7 activator Asiatic Acid (AA), for rebalancing TGF-β/Smad signalling in the TME, and its implication on the multidrug resistance is still unexplored. Here, we observed that an equilibrium shift of the Smad signalling in patients with hepatocellular carcinoma (HCC), which was dramatically enhanced in the recurrent cases showing p-glycoprotein overexpression. We optimized the formula ratio and dosage of AANG that effectively inhibit the proliferation of our unique human multidrug resistant subclone R-HepG2. Mechanistically, we found that AANG not only inhibits Smad3 at post-transcriptional level, but also upregulates Smad7 at transcriptional level in a synergistic manner in vitro. More importantly, AANG markedly suppressed the growth and p-glycoprotein expression of R-HepG2 xenografts in vivo. Thus, AANG may represent a novel and safe TCM-derived natural compound formula for overcoming HCC with p-glycoprotein-mediated multidrug resistance.

KEYWORDS

AANG, Asiatic acid, hepatocellular carcinoma, multidrug resistance, naringenin, p-glycoprotein, TGF-β/Smad signalling

Jeff Yat-Fai Chung and Max Kam-Kwan Chan are equally contributed to this work.

International Journal of
Molecular Sciences

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Review

TGF-β Signaling: From Tissue Fibrosis to Tumor Microenvironment

Jeff Yat-Fai Chung [1,†], Max Kam-Kwan Chan [1,†], Jane Siu-Fan Li [1,†], Alex Siu-Wing Chan [2], Philip Chiu-Tsun Tang [3], Kam-Tong Leung [3], Ka-Fai To [1], Hui-Yao Lan [4] and Patrick Ming-Kuen Tang [1,*]

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Abstract: Transforming growth factor-β (TGF-β) signaling triggers diverse biological actions in inflammatory diseases. In tissue fibrosis, it acts as a key pathogenic regulator for promoting immunoregulation via controlling the activation, proliferation, and apoptosis of immunocytes. In cancer, it plays a critical role in tumor microenvironment (TME) for accelerating invasion, metastasis, angiogenesis, and immunosuppression. Increasing evidence suggest a pleiotropic nature of TGF-β signaling as a critical pathway for generating fibrotic TME, which contains numerous cancer-associated fibroblasts (CAFs), extracellular matrix proteins, and remodeling enzymes. Its pathogenic roles and working mechanisms in tumorigenesis are still largely unclear. Importantly, recent studies successfully demonstrated the clinical implications of fibrotic TME in cancer. This review systematically summarized the latest updates and discoveries of TGF-β signaling in the fibrotic TME.

Keywords: TGF-β; tumor microenvironment; fibrosis

Citation: Chung, J.Y.-F.; Chan, M.K.-K.; Li, J.S.-F.; Chan, A.S.-W.; Tang, P.C.-T.; Leung, K.-T.; To, K.-F.; Lan, H.-Y.; Tang, P.M.-K. TGF-β Signaling: From Tissue Fibrosis to Tumor Microenvironment. *Int. J. Mol. Sci.* **2021**, *22*, 7575. https://doi.org/10.3390/ijms22147575

Academic Editor: A. Phillip West

Received: 24 May 2021
Accepted: 9 July 2021
Published: 15 July 2021

1. Introduction

Transforming growth factor-beta (TGF-β) was discovered as a versatile cytokine with both pathological and physiological functions. The main isoforms of the TGF-β family, TGF-β1, TGF-β2, and TGF-β3, show different biological activities [1,2]. Interestingly, only the promoter region of TGF-β1 can be activated directly by different trans-activating proteins such as reactive oxygen species (ROS), plasmin, and acid due to its multiple regulatory sites [3], highlighting its pleiotropic nature in fibrogenesis, carcinogenesis, immune modulation, cell proliferation, and differentiation [4,5].

The molecular pathways of TGF-β signaling have been studied extensively in various biological processes, including proliferation, differentiation, and apoptosis [6]. TGF-β signaling causes different downstream actions in a context dependent manner, especially in cancer. It plays a dual role, being both a tumor suppressor in pre-malignant cells and a tumor promoter in cancer cells, respectively [7]. Cancer cells are able to inactivate the tumor suppressive components of the TGF-β/Smad signaling through acquired mutations, while the tumor suppressive effects can exert selective pressure on the pre-malignant cells [8]. Indeed, cancer cells can also use the pleiotropic nature of TGF-β signaling and its downstream mediators to escape from the anti-tumor immunity by creating an immunosuppressive tumor microenvironment (TME) [8,9]. The TGF-β/Smad pathway mediates

International Journal of
Molecular Sciences

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Review

The Emerging Role of Innate Immunity in Chronic Kidney Diseases

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Received: 1 April 2020; Accepted: 2 June 2020; Published: 4 June 2020

Abstract: Renal fibrosis is a common fate of chronic kidney diseases. Emerging studies suggest that unsolved inflammation will progressively transit into tissue fibrosis that finally results in an irreversible end-stage renal disease (ESRD). Renal inflammation recruits and activates immunocytes, which largely promotes tissue scarring of the diseased kidney. Importantly, studies have suggested a crucial role of innate immunity in the pathologic basis of kidney diseases. This review provides an update of both clinical and experimental information, focused on how innate immune signaling contributes to renal fibrogenesis. A better understanding of the underlying mechanisms may uncover a novel therapeutic strategy for ESRD.

Keywords: chronic kidney disease; microenvironment; kidney fibrosis; macrophage–myofibroblast transition; inflammation

1. Introduction

Chronic kidney disease (CKD) is an emerging cause of morbidity and mortality worldwide. The global estimated prevalence of CKD is 13.4% (11.7%–15.1%) [1], affecting 26–30 million adults in the United States [2], 120 million adults in China, and causing renal replacement of 4.902 to 7.083 million patients. CKD defines as abnormalities of kidney structure or function caused by primary and secondary glomerular diseases, including glomerulonephritis, hypertension, and diabetic mellitus [3,4]. Notably, effective CKD treatment is still unavailable.

Glomerulosclerosis and tubulointerstitial fibrosis are core manifestations of CKD, considered as the common fate of most chronic and progressive nephropathies toward end-stage renal disease (ESRD). In glomerulosclerosis, mesangial and endothelial cells play an important role in extracellular matrix (ECM) production by forming myofibroblasts [5]. In contrast, renal tubular epithelial cells and infiltrating immunocytes largely contribute to the ECM formation in tubulointerstitial fibrosis [6–10]. It is conceivable that glomerulosclerosis and tubulointerstitial fibrosis share similar disease mechanisms with minor differences. In general, collagen type IV deposits in the mesangial interstitial space and manifests as nodular changes in the glomeruli, whereas collagen type I deposits and manifests as

Exploration of Targeted Anti-tumor Therapy

Open Exploration

Open Access Review

Transforming growth factor-β signaling: from tumor microenvironment to anticancer therapy

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Academic Editor: Fathia Mami-Chouaib, Université Paris-Saclay, France

Received: October 29, 2022 **Accepted:** February 9, 2023 **Published:** April 28, 2023

Cite this article: Chan MKK, Chan ELY, Ji ZZ, Chan ASW, Li C, Leung KT, et al. Transforming growth factor-β signaling: from tumor microenvironment to anticancer therapy. Explor Target Antitumor Ther. 2023;4:316–43. https://doi.org/10.37349/etat.2023.00137

Abstract

Transforming growth factor-β (TGF-β) signaling is an important pathway for promoting the pathogenesis of inflammatory diseases, including cancer. The roles of TGF-β signaling are heterogeneous and versatile in cancer development and progression, both anticancer and protumoral actions are reported. Interestingly, increasing evidence suggests that TGF-β enhances disease progression and drug resistance via immune-modulatory actions in the tumor microenvironment (TME) of solid tumors. A better understanding of its regulatory mechanisms in the TME at the molecular level can facilitate the development of precision medicine to block the protumoral actions of TGF-β in the TME. Here, the latest information about the regulatory mechanisms and translational research of TGF-β signaling in the TME for therapeutic development had been summarized.

Keywords

Transforming growth factor-β, tumor microenvironment, cancer, immunity, cancer immunotherapy

Introduction

Transforming growth factor-β (TGF-β) cytokine superfamily is composed of highly pleiotropic molecules, including TGF-β, activin, inhibin, bone morphogenetic protein (BMP), etc., which are important for regulating tissue inflammation, fibrosis, cell apoptosis, and proliferation [1]. TGF-β1, 2, and 3 have been defined as three isoforms of TGF-β in mammals [2]. They have been encoded as precursors with 70–80% homology and control

第7屆香港大學生創新及創業大賽

The 7th Hong Kong University Student Innovation and Entrepreneurship Competition

Centificate of Award

獎狀

Chung Jeff Yat Fai
Chan Max Kam Kwan

鍾一珲 陳金坤

awarded the Frist Prize of
Life Sciences of the Competition.

榮獲 生命科學 一等獎

Project: A Novel Neutrophil-based Anticancer Immunotherapy: S3KO-TAN

項目：一種基於中性粒細胞的新型抗癌免疫療法：S3KO-TAN

MAY 2021

二零二一年五月

資助機構 Funding Organization：

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获奖证书

香港中文大学

钟一珲、陈金坤 同学：

你们的作品《一种基于中性粒细胞的新型抗癌免疫疗法 S3KO-TAN》在第十七届“挑战杯”全国大学生课外学术科技作品竞赛中荣获

一等奖

指导教师：邓铭权

编号：2021-TZB17-MA11236H-1F1BB7

共青团中央 中央委员会 | 中国科协 | 教育部 | 中国社会科学院 | 全国学联 | 四川省人民政府

二〇二二年三月

DIPLÔME

Inventions Geneva

SALON INTERNATIONAL DES INVENTIONS GENÈVE

Après examen, le Jury a décidé

de remettre à: Patrick Ming-Kuen TANG, Hui-Yao LAN, Jeff Yat-Fai Chung, Philip Chiu-Tsun TANG, Max Kam-Kwan CHAN

pour l'invention: A Novel Neutrophil-based Anticancer Immunotherapy

MÉDAILLE DE BRONZE
BRONZE MEDAL
BRONZEMEDAILLE

Genève, le 28 mars 2022

Le Président du Jury: David Toji

Le Président du Salon: Jean-Luc Vincent

OFFICIAL (COMMERCIAL)

GRANT AGREEMENT

THIS AGREEMENT (the "Agreement") is dated/made on:
1 July 2022

PARTICULARS PAGE

PARTIES

(1) **HONG KONG SCIENCE AND TECHNOLOGY PARKS CORPORATION (香港科技園公司)**, a corporation formed under the Hong Kong Science and Technology Parks Corporation Ordinance (Cap. 565), of 5/F, Building 5E, Hong Kong Science Park, Shatin, New Territories, Hong Kong ("**Grantor**"); and

(2) The person/corporation mentioned below ("**Grantee**").

WHEREAS

The Grantor offers a pre-incubation support programme for tech-focused entrepreneurs known as **IDEATION (the "Programme")**. The Grantee wishes to participate in the Programme and the Grantor is willing to admit the Grantee into the Programme in accordance with the terms and conditions of this Agreement.

In consideration of the mutual promises and covenants contained in this Agreement, the Grantor and Grantee hereby agree to enter into this Agreement with the following particulars and agree to abide by the terms and conditions attached hereto.

1.	Name of person/corporation	CHAN KAM KWAN
2.	Address/Registered office	Room 508, 5/F, Block B, Kam Pong House, Kam Tai Court, Ma On Shan, New Territories, Hong Kong
3.	Incubation Centre	Lion Rock 72 at Innocentre ("LR72")
4.	Programme Period	12 months commencing from 1 July 2022 to 30 June 2023 (both days inclusive).
5.	Grants	The grants made available by the Grantor to the Grantee pursuant to this Agreement

第十三届“挑战杯”
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陈金坤 钟一辉 李昭勋 陈乐瑶 同学

你（们）的项目《天然中藥化合物組克服腫瘤耐藥性：AANG》

在第十三届“挑战杯”中国大学生创业计划竞赛中荣获

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特颁此证，以资鼓励。

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第十三届“挑战杯”中国大学生
创业计划竞赛全国组织委员会

第8屆香港大學生創新及創業大賽

The 8th Hong Kong University Student Innovation & Entrepreneurship Competition

獎狀

Certificate of Award

茲証明

This is to certify that

陳金坤 鍾一琿 李昭勳

Chan Kam Kwan, Chung Yat Fai, Li Siu Fan Jane

榮獲 生命科學 二等獎

awarded the Second Prize of
Life Sciences in the Competition

天然中藥化合物組克服腫瘤耐藥性：AANG

AANG: A Chinese Medicine Derived Natural Compound Formula for Overcoming Multidrug Resistance

11 · 2022

資助機構 Funding Organization：

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Hong Kong New Generation Cultural Association

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13

Where Inventors Meet Inventors

Bronze Medal Certificate

IIFME
International Invention Fair in the Middle East
المعرض الدولي للاختراعات في الشرق الأوسط
February 12 - 15, 2023

Kuwait Science Club

Under the Patronage of His Highness the Amir of the State of Kuwait

Sheikh Nawaf Al-Ahmad Al-Jaber Al-Sabah

hereby awards **BRONZE** medal to

TANG Ming Kuen Patrick, CHUNG Yat Fai Jeff, CHAN Kam Kwan Max

in recognition of excellence to invent

A Novel Neutrophil Anticancer Immunotherapy S3KO-TAN

showcased at the fair held on February 12 - 15, 2023

Talal Jassim Al-Kharafi
Chairman of Kuwait Science Club
Head of Higher Committee

DIPLÔME

Inventions Geneva

SALON INTERNATIONAL DES INVENTIONS GENÈVE

Après examen, le Jury International a décidé

de remettre à : **Prof. Patrick Ming Kuen TANG, Dr. Max Kam Kwan CHAN, Dr. Philip Chui Tsun TANG**

pour l'invention : **EDC-T : Une immunothérapie à base d'IA pour les cancers solides**

MÉDAILLE D'ARGENT
SILVER MEDAL
SILBERMEDAILLE

Genève, le 12 avril 2025

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Le Président du Salon: Jean-Luc Vincent

获奖证书

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作品名称：一种针对实体癌的新型高效 T 细胞疗法

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参赛学生：陈金坤、李昭勋、苟泽源、陈乐瑶

指导教师：邓铭权

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教育部、中央统战部、中央网信办、国家发展改革委、工业和信息化部、人力资源社会保障部、农业农村部、中国科学院、中国工程院、国家知识产权局、国家乡村振兴局、共青团中央、天津市人民政府

中国国际大学生创新大赛组委会

二〇二三年十二月

证书编号：202306617Z

第九屆中國國際「互聯網+」大學生創新創業大賽

茲證明

陳金坤 李昭勳 芶澤源 陳樂瑤

參賽項目：一種針對實體癌的新型高效T細胞療法

榮獲

銀獎

香港特別行政區組織機構：

香港新一代文化協會
Hong Kong New Generation Cultural Association

第9屆香港大學生創新及創業大賽

The 9th Hong Kong University Student Innovation and Entrepreneurship Competition

獎狀

CERTIFICATE OF AWARD

茲証明

This is to Certify that

陳金坤　苟澤源　李昭勳　陳樂瑤

Chan Kam Kwan, Ji Zeyuan, Li Siu Fan Jane
Chan Lok Yiu

榮獲 生命科學 二等獎

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Life Sciences in the Competition

一種針對實體癌的新型高效 T 細胞療法

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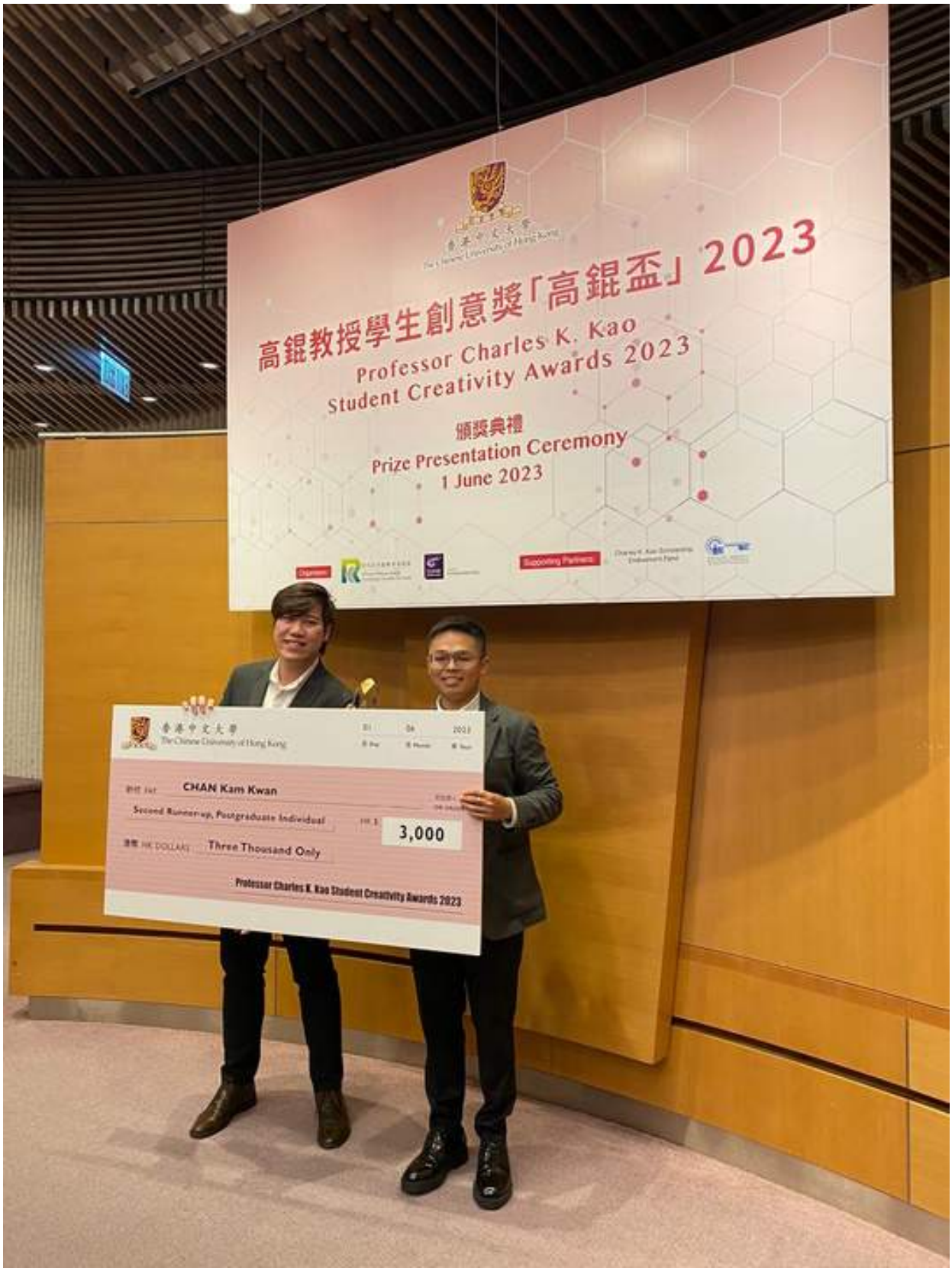
頒發日期: 06-2023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