Discover Oncology

Review

Vitamin A and its influence on tumour extracellular matrix

Guoqing Xie[1,2] · Shun Cao[1,2] · Guangchun Wang[3] · Xianzhong Zhang[4] · Yu Zhang[6] · Haofan Wu[4] · Shuxian Shen[4,5] · Jiandong Le[1,2] · Keqiang Li[2,3,5] · Zhenlin Huang[1]

Received: 2 October 2024 / Accepted: 2 January 2025
Published online: 07 January 2025

Abstract
Vitamin A is a crucial nutrient renowned for its role in visual health and cellular regulation. Its derivatives influence cell differentiation, proliferation, and tissue homeostasis, making them significant in cancer research due to their effects on both normal and tumour cells. This review explores the intricate relationship between vitamin A metabolism and the extracellular matrix (ECM) in cancer. The ECM profoundly affects tumour behaviour, including proliferation, invasion, and metastasis. Alterations in the ECM can facilitate tumour progression, and vitamin A derivatives have shown potential in modulating these changes. Through transcriptional regulation, vitamin A impacts ECM components and matrix metalloproteinases, influencing tumour dynamics. The review highlights the potential of vitamin A and its derivatives as adjunctive agents in cancer therapy. Despite promising laboratory findings, their clinical application remains limited due to challenges in translating these effects into therapeutic outcomes. Future research should focus on the modulation of retinol metabolism within tumours and the development of targeted therapies to enhance treatment efficacy and improve patient prognosis.

Keywords Vitamin A · Retinol · Retinoic acid · ECM · TME · Cancer therapy

1 Introduction

Vitamin A is an essential nutrient, universally acknowledged for its critical role in maintaining visual health [1, 2]. Beyond this, vitamin A and its derivatives are vital in regulating cellular differentiation, proliferation, and tissue homeostasis [3–5]. These compounds have attracted substantial interest in oncological research due to their capacity to modulate the biological behaviours of both normal and tumour cells.

Vitamin A and its metabolic products serve a multitude of functions; apart from their well-known role as precursors to visual pigments, they also play pivotal roles in the regulation of gene expression and cellular signalling pathways [3, 4, 6–8]. Furthermore, as a fat-soluble vitamin, the oxidative regulatory properties of vitamin A are indispensable in mechanisms that alter cellular biological behaviours [9, 10]. These include modulating DNA damage induced by oxidative stress and regulating ferroptosis, thereby influencing tumour progression [11–13].

Guoqing Xie, Shun Cao, Guangchun Wang and Xianzhong Zhang have contributed equally to this work and share first authorship.

✉ Keqiang Li, lz1996998@gmail.com; ✉ Zhenlin Huang, hzlinok@outlook.com | [1]Department of Urology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan Province, China. [2]Academy of Medical Sciences, Zhengzhou University, Zhengzhou, Henan Province, China. [3]Department of Urology, Shanghai Tenth People's Hospital, Tongji University School of Medicine, Shanghai, China. [4]Department of Gastrointestinal Surgery, Shanghai Tenth People's Hospital, Tongji University School of Medicine, Shanghai, China. [5]School of Medicine, Cancer Institute, Tongji University, Shanghai, China. [6]Department of Urology, the First Affiliated Hospital of Peking University, Beijing, China.

Alterations in the ECM profoundly impact cancer cell behaviour, including proliferation, invasion, and metastasis. The ECM provides structural support and serves as a crucial medium for intercellular signalling, thus maintaining tissue stability and function. Within the cancer microenvironment, changes in the ECM's composition, structure, and mechanical properties often promote malignant behaviour [14–16]. For instance, cancer cells can undermine the integrity of the basement membrane through matrix metalloproteinases (MMPs), creating conditions favourable for invasion and metastasis [17]. Moreover, alterations in the basement membrane composition can activate surrounding normal cells and immune cells, triggering a cascade of signalling events that promote tumour cell survival and proliferation [18, 19]. Consequently, the regulation of the composition and function of the ECM continues to be a central focus in cancer research. Numerous studies are investigating how modulation of the ECM's dynamic equilibrium can restrain tumour invasiveness and metastatic potential.

Emerging evidence suggests complex interactions between vitamin A metabolism and ECM regulation in cancer. Vitamin A derivatives have been shown to modulate the expression of MMPs and ECM components such as type IV collagen, thereby altering the ultrastructure of the basement membrane. However, these effects may vary due to other factors [20–22].

Consequently, understanding the interplay between vitamin A metabolism and tumour ECM is paramount. Firstly, given the critical role of tumour metabolic reprogramming in the progression of cancer, exploring this relationship could provide novel insights into the mechanisms through which vitamin A influences tumour prognosis. Secondly, elucidating this relationship could reveal new therapeutic targets or strategies for cancer treatment. Currently, vitamin A and its derivatives are considered potential adjunctive agents in cancer therapy. The convenience of vitamin supplementation and its widespread acceptance among patients make it an appealing approach for chemoprevention and treatment of various cancers, including melanoma. However, the clinical application of vitamin A and its derivatives in cancer therapy still requires a comprehensive understanding of its impact on the tumour microenvironment, particularly the ECM.

This review aims to elucidate the complex relationship between vitamin A metabolism and the tumour ECM. We particularly highlight how an overall dysregulation of vitamin A (retinol) metabolism, rather than merely circulating retinol levels, may have a more significant impact on tumour prognosis.

2 Vitamin A metabolism

2.1 Vitamin A as an essential nutrient

Vitamin A was discovered between 1912 and 1914 by American scientists Elmer McCollum and Margaret Davis [23]. It is not a single compound but a series of retinol derivatives, including retinol, retinal, retinoic acid (RA), retinyl acetate, and retinyl palmitate. Vitamin A is found only in animal sources, though many vegetables and fruits contain carotenoids that can be converted into vitamin A in the intestine.

Vitamin A is crucial for human health and has long been recognized as an essential dietary supplement. It plays a crucial role in a myriad of essential human functions, from vision to skin health, from bone development to maintaining reproductive functions. Specifically, in vision, vitamin A participates in the synthesis and cycling of rhodopsin in the retina, which is essential for low-light vision [7]. In the skin and mucous membranes, vitamin A maintains the integrity and function of epithelial cells, whose deficiency can lead to cell keratinisation, dryness, and impaired function [24, 25]. Vitamin A also regulates the immune system by modulating the differentiation and function of immune cells, enhancing the body's antiviral and anti-tumour capabilities [26, 27]. Additionally, vitamin A plays a significant role in growth and development, influencing bone and tooth development through calcium metabolism, regulating the formation of sperm and follicles, and affecting the secretion of sex hormones for normal reproductive function [28, 29]. Furthermore, vitamin A enhances iron absorption and production by increasing the number of iron transport proteins on the surface of intestinal cells, releasing stored iron in the liver, and synthesizing ferritin [30, 31].

2.2 Absorption and metabolism of vitamin A

The absorption of vitamin A primarily occurs in the small intestine where dietary retinyl esters are hydrolysed into retinol. This hydrolysis is catalysed by pancreatic triglyceride lipase and carboxyl ester lipase, both of which require bile salts for optimal activity. Once hydrolysed, retinol is taken up by intestinal epithelial cells largely through active mechanisms facilitated by enzymes and bile salts. Inside these cells, retinol is re-esterified to retinyl esters, which are then packaged into

chylomicrons for distribution via the lymphatic system to the rest of the body. The transport and distribution of vitamin A are predominantly mediated by these chylomicrons, which carry retinyl esters primarily to the liver, the central organ for vitamin A storage and metabolism. In the liver, retinyl esters are enzymatically cleaved to release free retinol, which then binds to retinol-binding protein. This complex facilitates the transport of retinol to various target tissues through the bloodstream [32, 33]. Additionally, the transport of retinol between cells and the extracellular fluid is regulated by mechanisms including endocytosis and release, which are mediated by the STRA6 receptor [34].

In cancer patients, the metabolism of vitamin A can be significantly altered, affecting not only the basic nutritional status of the patient but also disease progression and treatment outcomes. The most significant impact is seen in patients with digestive system cancers. Whether it is liver, stomach, or small intestine cancer, it can cause vitamin A absorption disorders, which are related to the interactions (feedback regulation) between digestive system organs. Additionally, corresponding surgical procedures and chemotherapy can further cause gastrointestinal damage, affecting the absorption and transport processes of vitamin A, leading to decreased serum vitamin A levels [35, 36].

The intracellular retinol metabolic pathway is a complex and precise biochemical process involving the coordinated action of various key enzymes and proteins. Retinol dehydrogenase (RDH), alcohol dehydrogenase (ADH), Dehydrogenase/Reductase (SDR family) Members (DHRS), aldehyde dehydrogenase (ALDH), and Aldo–Keto reductase (AKR) are core enzymes involved in the redox of retinol. RDH and ADH primarily oxidize retinol to retinal, which is the first critical step in vitamin A metabolism. ALDH further oxidizes retinal to RA, the main active metabolite of vitamin A. AKR and DHRS play a bidirectional catalytic role in the conversion between retinal and retinol, crucial for maintaining the balance of retinol metabolism [37, 38]. Changes in the activity and expression levels of these enzymes can lead to abnormal retinol metabolism, affecting various physiological processes and the development of diseases (Fig. 1).

3 Interactions between vitamin A metabolism and tumour ECM

3.1 Molecular mechanisms of retinoids and their therapeutic potential in cancer

For a long time, vitamin A and its derivatives have primarily been utilised as nutrients. However, they also participate in various intracellular and intercellular molecular mechanisms in the form of different derivatives [26, 27, 39, 40]. Vitamin A, predominantly via its active metabolite all-trans retinoic acid (ATRA), plays a crucial role in modulating gene expression by interacting with nuclear receptors. These receptors include retinoic acid receptors (RARs) and retinoid X receptors (RXRs), which function as ligand-dependent transcription factors. Upon binding with ATRA, RAR/RXR heterodimers are formed, which then attach to retinoic acid response elements (RAREs) located in the promoters of target genes. This interaction facilitates the recruitment of co-activators or the release of co-repressors, leading to the regulation of transcription [41–43].

Beyond its genomic effects, vitamin A initiates non-genomic signalling pathways, including the activation of mitogen-activated protein kinase (MAPK) cascades [44–46]. These extranuclear effects occur through interactions with RARs at the cell membrane, activating kinase pathways that lead to the phosphorylation of transcription factors and subsequent modulation of gene expression. Furthermore, recent advancements have revealed that vitamin A, independent of ATRA, can directly activate the Janus kinase (JAK)/STAT5 pathway, broadening its biological functions [47]. This complex array of mechanisms highlights vitamin A's multifaceted role, influencing processes such as cellular differentiation, metabolism, immunity, and overall physiological homeostasis throughout development and across different tissues. Similarly, various derivatives of vitamin A exert therapeutic effects on tumours by regulating tumour cell survival, growth, cell cycle distribution, and gene expression through the aforementioned molecular mechanisms.

Notably, ATRA has been proven to effectively reverse the progression of specific types of leukaemia, such as acute promyelocytic leukaemia (APL), through its powerful cell differentiation and anti-proliferative properties [48, 49]. It is worth noting that in large cohort Mendelian studies, circulating retinol has not shown a significant relationship with tumour prognosis [50]. However, some studies targeting specific groups have found that circulating retinol levels can influence some tumour prognosis, and the conclusions of these studies are often inconsistent, highlighting the complexity of the role of vitamin A as a basic nutrient in cancer and other diseases [51–59].

Despite these conflicting findings, vitamin A and its derivatives are explicitly recommended in clinical guidelines for various types of cancer. For instance, ATRA is well known for inducing differentiation therapy in APL, and bexarotene is employed to treat relapsed or refractory cutaneous T-cell lymphoma [60, 61]. Unfortunately, although numerous studies indicate that vitamin A derivatives and analogues can improve tumour prognosis, most focus on retinoic acid drugs, and

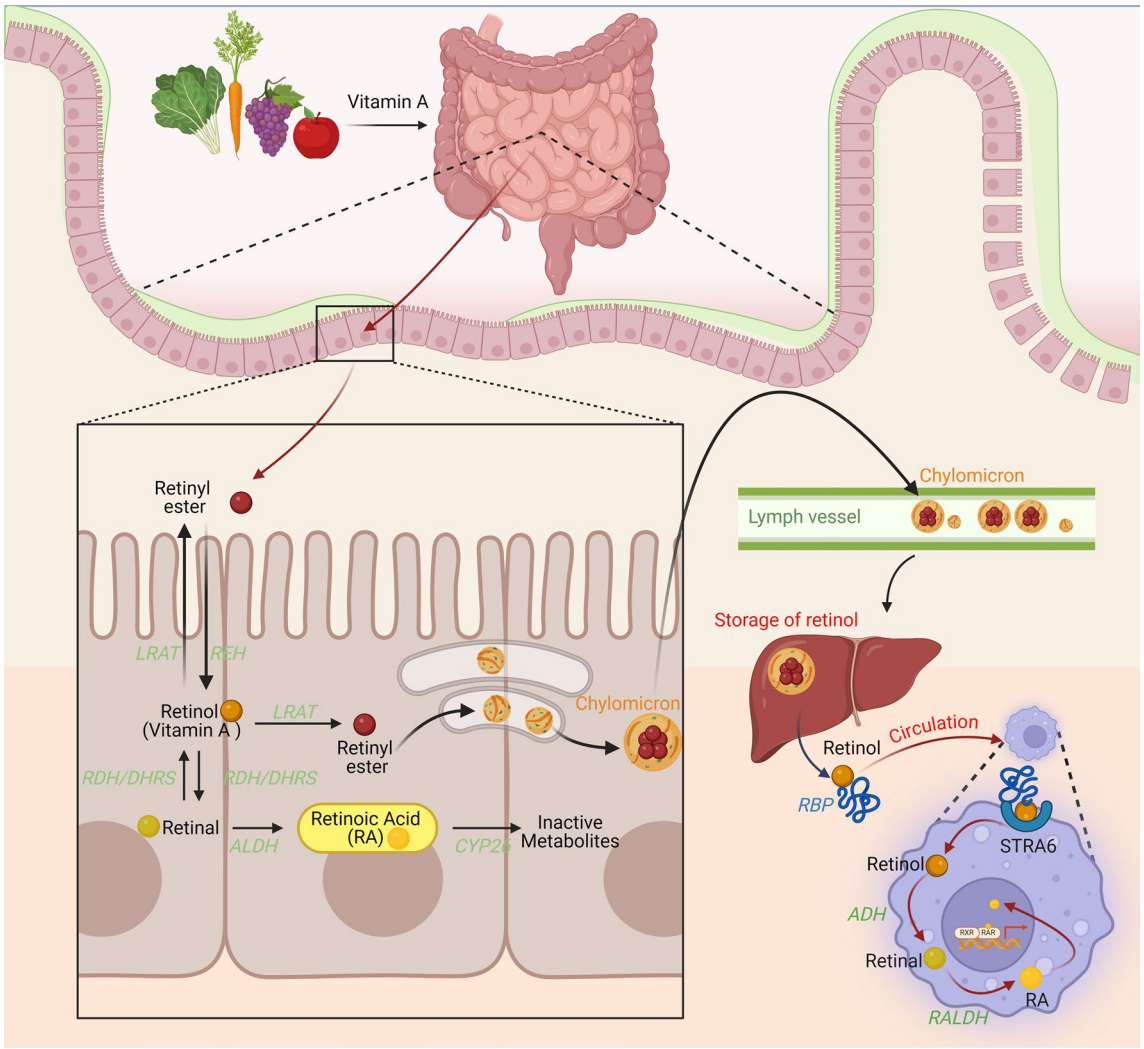

Fig. 1 Absorption and intracellular metabolism of vitamin A

the therapeutic effects observed in these cohort studies vary considerably in some aspects. Overall, current research on the impact of vitamin A metabolism and its derivatives on the tumour ECM to enhance tumour prognosis remains predominantly at the laboratory stage and has not been widely applied in clinical practice.

Furthermore, retinol and its derivatives can indirectly affect tumours by modulating the immune system. Interest in vitamin A as a modulator of immune function dates back to the early 1900s. First-generation retinoid compounds such as 13-cis-retinoic acid (13-cRA), second-generation compounds like 9-cis-retinoic acid (9-cRA), and third-generation retinoids such as bexarotene have been proven to exert partial or full anticancer effects through immunomodulation [62–69]. Although existing studies show that retinol and its derivatives can regulate nearly all aspects of the immune system, current research primarily focuses on their regulation of T-cell proliferation and differentiation and their role as cofactors in various immune functions. TLR2 signalling induces splenic dendritic cells to express RA-metabolising enzymes like ALDH1A2 and IL-10, promoting T cell responses that enhance FOXP3 + regulatory T cell (Treg) generation while inhibiting Th17 differentiation [70, 71]. In addition, Z. Wang et al. discovered that RA can regulate the expression of ICAM-1 [72], while RA-treated UM cells exhibit increased sensitivity to MHC class I-restricted cytotoxic T lymphocyte killing and NK cell-mediated lysis [73]. Additional research suggested that ATRA enhances the efficacy of anti-PD-1 therapy by targeting myeloid-derived suppressor cells (MDSCs) [74]. Meanwhile, Ziyi Peng et al. revealed that NSD2 interacts with RARα, not only enhancing RARα nuclear condensation but also regulating histone H3K36 dimethylation at the CD38 promoter, thereby upregulating CD38 expression in multiple myeloma cells [75].

In summary, vitamin A and its metabolites enhance antitumour immune responses in the tumour microenvironment by regulating immune cell differentiation and function.

It is also important to note that although vitamin A often functions as a nutrient, excessive intake can cause severe harm to the body. Acute toxicity can result from the ingestion of 100,000 IU (1 IU = 0.3 μg) of vitamin A over a short period, while chronic toxicity may occur from daily intakes exceeding 10,000 IU. Specific clinical manifestations include acute symptoms such as nausea, vomiting, and dizziness, as well as long-term damage symptoms including liver damage, reduced red blood cells, bone pain, visual disturbances, and neurological abnormalities. Retinoic acid syndrome is also a manifestation of the toxicity of vitamin A derivatives [76–79] (Fig. 2).

3.2 Vitamin A's impact on ECM in tumours

Vitamin A, in addition to its immunomodulatory effects and its role in promoting terminal differentiation, inhibiting proliferation, and inducing apoptosis in tumour cells, also uniquely influences the ECM, which is another important way in which vitamin A and its derivatives influence the biological behaviour of tumour cells [26, 27, 39, 40].

In the tumour microenvironment, the ECM provides structural support and regulates processes like tumour cell proliferation, migration, invasion, and resistance to apoptosis through interactions with cell receptors [16, 17, 80–83].

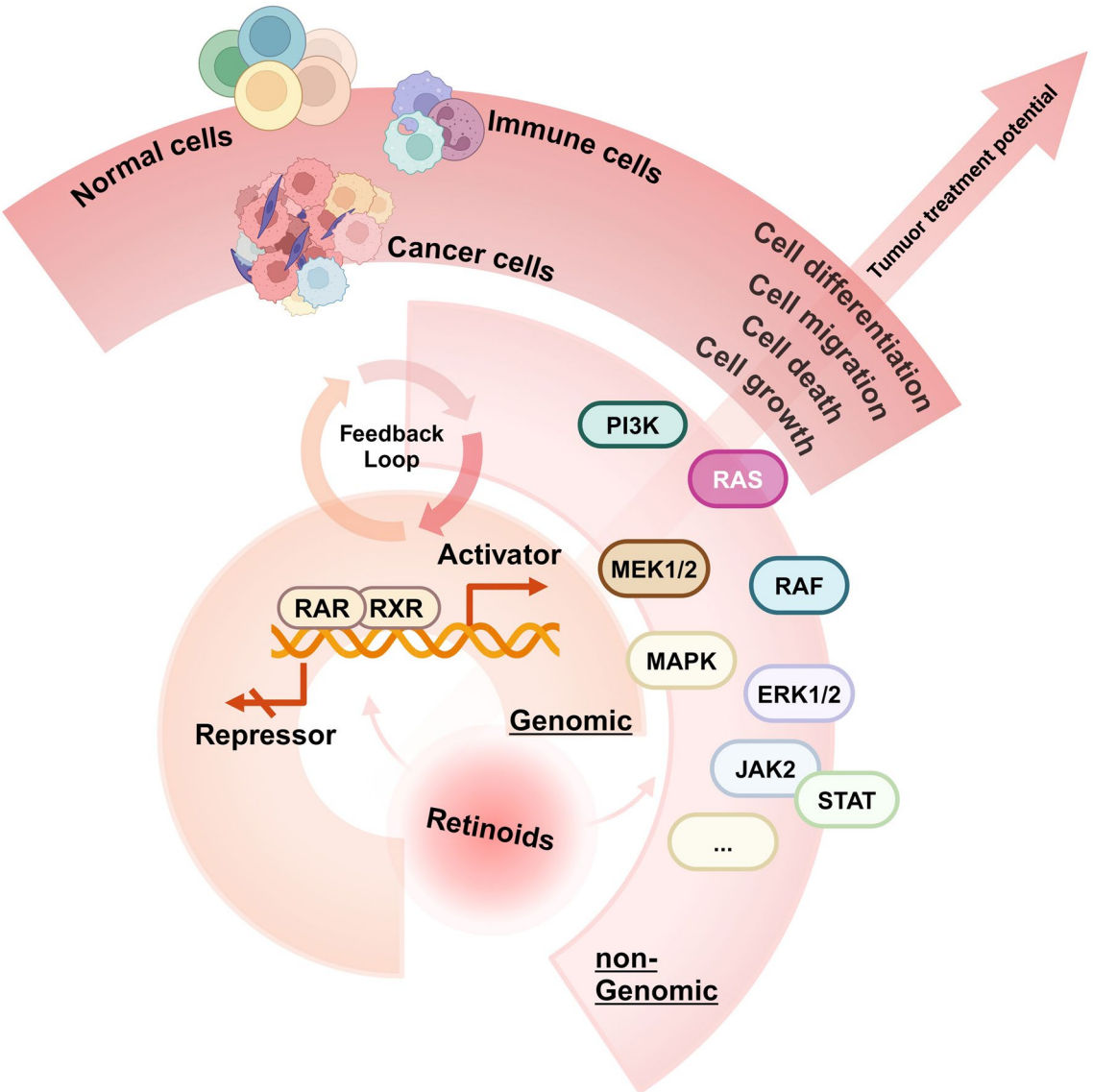

Fig. 2 Main molecular mechanisms of vitamin A and its derivatives in cells

The ECM is constantly remodelled by tumour and stromal cells, with enzymes degrading it and releasing growth factors that drive invasion and metastasis [80, 84]. Additionally, the ECM acts as a barrier, limiting immune cell infiltration and aiding immune evasion [85, 86]. These roles make the ECM a key target in cancer therapy, with strategies focusing on inhibiting MMPs, targeting CAFs, and altering the ECM's biomechanical properties [87–89]. As our understanding of the ECM's role in cancer deepens, ECM-targeted therapies—particularly involving Vitamin A and its derivatives—are showing promise for cancer treatment.

The impact of vitamin A and its metabolic products on the ECM is mainly achieved through transcriptional regulation, which includes both direct and indirect effects. The direct effects are primarily realized through RA's direct transcriptional regulation of ECM components, such as influencing collagen synthesis, a major component of the ECM. Guillermo Esteban-Pretel et al. observed that vitamin A deficiency alters the subunit composition of collagen IV and laminin, as well as the proteolytic potential of lung tissue, while retinoic acid partially restores these changes [90]. Additionally, Studies have shown that ATRA reduces the expression and activity of MMP-2 and MMP-9, the enzymes responsible for ECM degradation, thereby inhibiting excessive ECM degradation and reducing cellular invasiveness [91, 92]. Research shows that in human foetal palatal mesenchymal cells (hFPMCs), excessive exposure to RA suppresses the mRNA and protein expression levels of various ECM components, including fibronectin, tensin C, and fibrillin-2, and this suppressive effect is dose-dependent and closely related to RA's transcriptional regulation [93–95].

RA also indirectly influences the ECM through signal transduction by regulating the expression of specific inflammatory factors, affecting the synchronous adjustment of ECM components. RA can affect the TGF-β/Smad signalling pathway, indirectly regulating ECM gene expression. Specifically, RA treatment significantly increases the expression of Smad7 and reduces the levels of TGF-β1, TGF-β3, and the TGF-β type II receptor, as well as reducing the phosphorylation levels of Smad2 and Smad3. Since TGF-β is a key regulator of ECM synthesis and degradation, RA regulates TGF-β activity, indirectly affecting the expression of ECM-related genes. It is worth noting that RA's transcriptional regulation of ECM genes may vary depending on cell type and growth conditions, highlighting the complexity and specificity of RA's regulation of the ECM. Moreover, RA can also inhibit ECM changes caused by TNF-α, achieved by inhibiting the JNK pathway and miRNA221 [96–98]. Additionally, from a chemical composition standpoint, vitamin A, a lipid-soluble vitamin, naturally exhibits capabilities for oxidative regulation, which help reduce damage caused by reactive oxygen species (ROS) [99]. This attribute plays a crucial role in preserving the structure and function of the extracellular matrix, particularly in environments characterised by oxidative stress.

Lineage plasticity refers to the ability of cells to change their fate or function under certain conditions, allowing them to transform into different cell types [100–102]. In some cases, excessive ECM deposition can lead to fibrosis, forming a dense ECM barrier [103, 104]. This not only alters the behaviour of tumour cells but also hinders the penetration of chemotherapy drugs. Retinoic acid, a derivative of vitamin A, helps reduce fibrosis by inhibiting the excessive conversion of activated stellate cells into myofibroblasts within the pancreatic tumour microenvironment. This, in turn, decreases the production of collagen and other ECM components, thereby improving the permeability of chemotherapy drugs in the tumour microenvironment [105].

Given the ECM's significant role in every stage of tumour progression, therapeutic strategies targeting the tumour ECM have emerged as a new research area. For example, CAFs, as an important component of the TME, promote tumour growth, invasion, and metastasis by secreting various factors and create physical barriers that hinder the entry of anti-cancer drugs and immune cells. Retinol metabolic products, such as all-trans retinoic acid, can maintain and transform CAFs into a quiescent state, disrupting the signal transduction between CAFs and tumour cells, thereby inhibiting tumour growth and metastasis. In certain cancer types, ATRA can interfere with tumour cell adhesion to the ECM by downregulating integrin expression, thus impeding their invasive behaviour within the ECM. For instance, research by S. L. Hsu et al. demonstrated that the cleavage of integrin α5β1 and focal adhesion kinase proteins is linked to the early stages of ATRA-induced apoptosis [106]. In this context, research on the retinoid Fenretinide has also demonstrated its unique therapeutic effects [107, 108]. Fenretinide can inhibit the activity of MMPs through the JNK pathway, thereby preventing ECM degradation and effectively reducing tumour invasion of the basement membrane [109, 110].

Most influences are reciprocal, and it is noteworthy that the ECM also affects the absorption and metabolism of vitamin A, exemplified by elements such as heparan sulphate proteoglycans (HSPGs), hyaluronic acid, and various modulators. As previously indicated, retinol requires binding with cholesterol micelles for transportation within the internal environment. The degree of sulfation of HSPGs is a primary determinant in the removal of residues from cholesterol micelles, thereby also impacting the clearance of retinol associated with these micelles. Hyaluronic acid and retinol can interact effectively; hyaluronic acid may facilitate the intercellular transfer and absorption of retinol and retinoic acid by improving

cellular channels and permeability, though this facilitating role is frequently utilised in drug delivery systems. Additionally, the ECM comprises various receptors and glycoproteins that are deeply involved in intracellular signalling pathways, undoubtedly influencing retinol metabolism within cells. Regrettably, research in this field is scant.

Overall, vitamin A and its derivatives show considerable potential in targeted therapy for tumour ECM, but their actual application still faces challenges: laboratory research and initial clinical trials have shown significant anti-tumour effects in some tumour types, but the effectiveness of its application lacks extensive validation, and the impact of vitamin A and its derivatives is inherently complex. From a historical scientific perspective, both issues have been present at the inception of research directions in scientific studies. Consequently, this demands that researchers prioritise addressing the principal issues during the initial stages (such as how RA "principally" influences ECM, as previously described). This approach aims to broaden interest among researchers in this field and to encourage the expansion of further studies (Fig. 3).

4 Discussion

4.1 Challenges in the application of retinoid drugs

Currently, the retinoid pharmaceuticals available on the market, excluding nutritional supplements, primarily consist of various types of RAs and their analogues. This trend is intimately associated with their early discovery, which demonstrated a significant improvement in the prognosis for patients with APL accompanied by minimal side effects. Although the treatment effects are significant, the lack of understanding of the mechanisms by which these drugs treat diseases at the time has limited further improvement in efficacy and deepened understanding of APL. Therefore, a large amount of research has begun to focus on derivatives centred on RA. As a result, the mechanisms of RA and its derivatives are now well understood. Against the backdrop of various laboratory mechanism studies and the inherent safety of this class of drugs, many doctors and researchers have also started to apply RA and its derivatives to diseases such as breast cancer and psoriasis. It is also essential to identify that many RA derivatives have been approved by drug administrative authorities around the world, and doctors and patients have a high

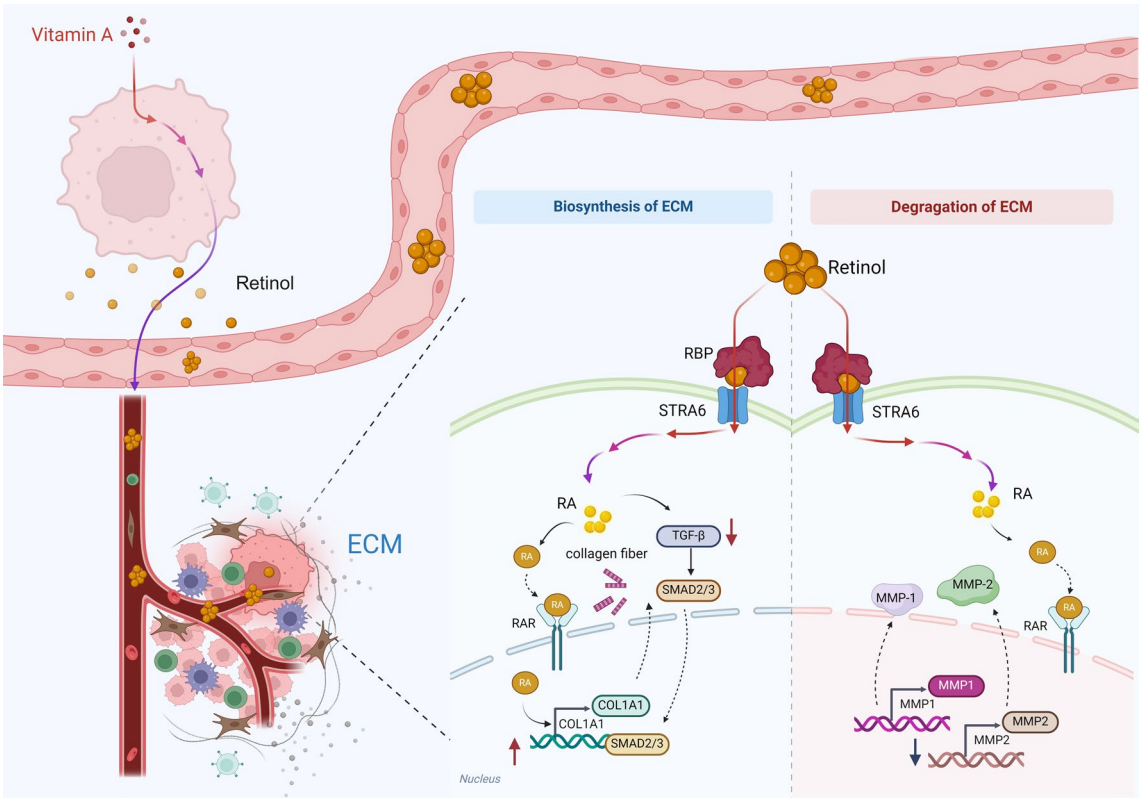

Fig. 3 Vitamin A metabolism and tumour ECM

acceptance and trust in these approved drugs, which has also promoted their application in other diseases. However, current clinical studies on RA treatment for malignant tumours excluding blood diseases have not made significant progress and have rarely been incorporated guidelines. This is mainly because RA drugs have much less tumouricidal ability compared to traditional chemotherapy drugs, and their impact on tumour cell growth and differentiation is more indirect. Therefore, current clinical trials of RA drugs in tumours mainly involve combination therapy.

On the other hand, a large amount of laboratory research shows that RA drugs can affect the TEM. However, how to transition this impact from laboratory research to clinical application is a challenge. Firstly, the pharmacokinetic process by which drugs travel through the bloodstream to the vicinity of tumour cells is complex. During the maintenance of therapeutic drug concentrations, although the side effects of RA drugs are significantly less severe than those of traditional chemotherapy agents, these effects cannot be overlooked. Moreover, in such cases, RA drugs often require combination with other chemotherapeutic drugs that have proven efficacy to achieve therapeutic objectives. And it is also crucial to note that mediating the tumour microenvironment by affecting the ECM is more of a prolonged and continuous process. Single-dose or periodic medication regimens are unlikely to make substantial improvements in the overall survival outcome by mediating the TME.

4.2 The potential of retinol metabolism studies in tumours

As mentioned in Sect. 4.1, recent large cohort Mendelian studies have found no significant relationship between circulating retinol levels and tumour prognosis. However, prior to this, some studies targeting specific groups found that circulating retinol levels can influence tumour prognosis, and these smaller cohort studies often have inconsistent conclusions. Undoubtedly, this underscores the complexity of the relationship between vitamin A and cancer, yet it is important for us to understand that studies on circulating retinol levels and retinol metabolism represent distinct research directions in understanding the influence on tumour biology and prognosis. And these cohort studies that focus on the relationship between circulating retinol and cancer predominantly adopt nutritional and etiological perspectives, particularly as these studies do not consider the availability of retinol in target tissues, such as factors affecting retinol's entry into cells (like the STRA6 receptor) and its esterification for storage (like phosphatidylcholine retinol acyltransferases). Consequently, these studies on circulating retinol do not discount the potential for modulating aberrant retinol metabolism and the effects of retinol and its derivatives on the biological behaviour of cancer cells. This is analogous to the well-known phenomenon in which cellular iron overload in tumour cells leads to the accumulation of ROS and promotes apoptosis, a process termed ferroptosis. However, this does not mean that supplementing iron to increase circulating iron levels will significantly affect tumour prognosis.

Therefore, focusing on the abnormalities in retinol metabolism within tumour cells, rather than circulating retinol levels, is crucial for future research into the impact of vitamin A and its derivatives on tumour prognosis. Developing modulators of key enzymes in retinol metabolism, or directly using gene-regulating drugs (such as ASO drugs), to reverse the abnormal state of retinol metabolism in tumour cells, represents a highly promising research direction. Additionally, the impact of widely accepted cancer treatment drugs on retinol metabolism is also worth further evaluation. For instance, our recent studies have found that TKIs significantly affect retinol metabolism, influencing the biological behaviour of tumour cells. These new insights will help advance understanding of drug mechanisms and improve patient outcomes through well-designed polypharmacy. Moreover, from a pathological perspective, by integrating metabolic characteristics, we will be able to make more precise judgments about tumour prognosis and medication, enhancing the efficiency of cancer treatment.

5 Method

A literature review was performed using the PubMed database to identify relevant studies on the complex interplay between vitamin a metabolism and extracellular matrix in cancer. The search was conducted from January 2000 to January 2024, and keywords such as vitamin A, vitamin A metabolism, retinol, retinoic acid, RA, tumours/cancers, extracellular matrix, tumour microenvironment, etc. were used to retrieve relevant articles. Using a database of search terms, a comprehensive search strategy was implemented to identify relevant studies for the literature review on the complex interplay between vitamin a metabolism and extracellular matrix in cancer.

To ensure the quality of the literature, papers presenting data in the form of letters, editorials, study protocols, case reports, short communications and articles not published in English were excluded. Colleagues examined the literature of all included papers for additional studies of interest. On this basis, and reflecting the long history of research on vitamins, 11 articles published before January 2000 and 3 article published after January 2024 were included.

Five independent researchers (two oncology researchers, two nutrition researchers, and one metabolism researcher) were consulted for each study considered for inclusion in the analysis. If three researchers provided negative comments on a particular study, it was excluded from the final selection.

Acknowledgements We thank Professor Yinghui Ding, Professor Chengle Zhuang and Professor Lin Sun for for resolving our queries on several key issues. The figure is created by Biorender, we thank for their brilliant work.

Author contributions Conception: GQX, KQL, ZLH Interpretation or analysis of data: GQX, ZLH, JDL Preparation of the manuscript: GQX, KQL, YZ, SC Revision for important intellectual content: KQL, ZLH, HHW, XZZ, SSX Supervision: ZLH, KQL, GCW. All co-authors have consented to the version of the manuscript for publication.

Funding This work was supported by the National Natural Science Foundation of China (no. 82303032 no. 82270809).

Data availability No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate Not applicable.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

References

1. Olson JA. Vitamin A deficiency. Nutr Rev. 1986;44(3):121–4.
2. Bates CJ. Vitamin A. Lancet. 1995;345(8941):31–5.
3. Blaner WS. Vitamin A signaling and homeostasis in obesity, diabetes, and metabolic disorders. Pharmacol Ther. 2019;197:153–78.
4. Janesick A, Wu SC, Blumberg B. Retinoic acid signaling and neuronal differentiation. Cell Mol Life Sci. 2015;72(8):1559–76.
5. Takahashi N, Saito D, Hasegawa S, Yamasaki M, Imai M. Vitamin A in health care: suppression of growth and induction of differentiation in cancer cells by vitamin A and its derivatives and their mechanisms of action. Pharmacol Ther. 2022;230: 107942.
6. Harris WA, Ready DF, Lipson ED, Hudspeth AJ, Stark WS. Vitamin A deprivation and Drosophila photopigments. Nature. 1977;266(5603):648–50.
7. Noell WK, Delmelle MC, Albrecht R. Vitamin A deficiency effect on retina: dependence on light. Science. 1971;172(3978):72–5.
8. Ghyselinck NB, Duester G. Retinoic acid signaling pathways. Development. 2019. https://doi.org/10.1242/dev.167502.
9. Blaner WS, Shmarakov IO, Traber MG. Vitamin A and Vitamin E: will the real antioxidant please stand up? Annu Rev Nutr. 2021;41:105–31.
10. Palace VP, Khaper N, Qin Q, Singal PK. Antioxidant potentials of vitamin A and carotenoids and their relevance to heart disease. Free Radic Biol Med. 1999;26(5–6):746–61.
11. de Lima-Reis SR, Silva TA, Costa LSA, Volp ACP, Rios-Santos F, Reis EM, Bassi-Branco CL. Serum levels of vitamin A, selenium, and better dietary total antioxidant capacity are related to lower oxidative DNA damage: a cross-sectional study of individuals at cardiovascular risk. J Nutr Biochem. 2022;107: 109070.
12. Murata M, Kawanishi S. Oxidative DNA damage by vitamin A and its derivative via superoxide generation. J Biol Chem. 2000;275(3):2003–8.
13. Jakaria M, Belaidi AA, Bush AI, Ayton S. Vitamin A metabolites inhibit ferroptosis. Biomed Pharmacother. 2023;164: 114930.
14. Kalluri R. The biology and function of fibroblasts in cancer. Nat Rev Cancer. 2016;16(9):582–98.
15. Mohan V, Das A, Sagi I. Emerging roles of ECM remodeling processes in cancer. Semin Cancer Biol. 2020;62:192–200.

16. Winkler J, Abisoye-Ogunniyan A, Metcalf KJ, Werb Z. Concepts of extracellular matrix remodelling in tumour progression and metastasis. Nat Commun. 2020;11(1):5120.
17. Kessenbrock K, Plaks V, Werb Z. Matrix metalloproteinases: regulators of the tumor microenvironment. Cell. 2010;141(1):52–67.
18. Mackel AM, DeLustro F, DeLustro B, Fudenberg HH, LeRoy EC. Immune response to connective tissue components of the basement membrane. Connect Tissue Res. 1982;10(3–4):333–43.
19. Vallejo J, Duner P, To F, Engelbertsen D, Goncalves I, Nilsson J, Bengtsson E. Activation of immune responses against the basement membrane component collagen type IV does not affect the development of atherosclerosis in ApoE-deficient mice. Sci Rep. 2019;9(1):5964.
20. Lackey DE, Hoag KA. Vitamin A upregulates matrix metalloproteinase-9 activity by murine myeloid dendritic cells through a nonclassical transcriptional mechanism. J Nutr. 2010;140(8):1502–8.
21. Vo HVT, Nguyen YT, Kim N, Lee HJ. Vitamin A, D, E, and K as matrix metalloproteinase-2/9 regulators that affect expression and enzymatic activity. Int J Mol Sci. 2023;24(23): 17038.
22. Varani J, Warner RL, Gharaee-Kermani M, Phan SH, Kang S, Chung JH, Wang ZQ, Datta SC, Fisher GJ, Voorhees JJ. Vitamin A antagonizes decreased cell growth and elevated collagen-degrading matrix metalloproteinases and stimulates collagen accumulation in naturally aged human skin. J Invest Dermatol. 2000;114(3):480–6.
23. McCollum E, Davis M. The essential factors in the diet during growth. J Biol Chem. 1915;23(1):231–46.
24. Roels OA, Anderson OR, Lui NS, Shah DO, Trout ME. Vitamin A and membranes. Am J Clin Nutr. 1969;22(8):1020–32.
25. Szymanski L, Skopek R, Palusinska M, Schenk T, Stengel S, Lewicki S, Kraj L, Kaminski P, Zelent A. Retinoic acid and its derivatives in skin. Cells. 2020. https://doi.org/10.3390/cells9122660.
26. Amimo JO, Michael H, Chepngeno J, Raev SA, Saif LJ, Vlasova AN. Immune impairment associated with vitamin A deficiency: insights from clinical studies and animal model research. Nutrients. 2022. https://doi.org/10.3390/nu14235038.
27. Mora JR, Iwata M, von Andrian UH. Vitamin effects on the immune system: vitamins A and D take centre stage. Nat Rev Immunol. 2008;8(9):685–98.
28. Clagett-Dame M, Knutson D. Vitamin A in reproduction and development. Nutrients. 2011;3(4):385–428.
29. Hogarth CA, Griswold MD. The key role of vitamin A in spermatogenesis. J Clin Invest. 2010;120(4):956–62.
30. Michelazzo FB, Oliveira JM, Stefanello J, Luzia LA, Rondo PH. The influence of vitamin A supplementation on iron status. Nutrients. 2013;5(11):4399–413.
31. Mehdad A, Siqueira EM, Arruda SF. Effect of vitamin A deficiency on iron bioavailability. Ann Nutr Metab. 2010;57(1):35–9.
32. Harrison EH. Mechanisms of digestion and absorption of dietary vitamin A. Annu Rev Nutr. 2005;25:87–103.
33. Reboul E. Absorption of vitamin A and carotenoids by the enterocyte: focus on transport proteins. Nutrients. 2013;5(9):3563–81.
34. Amengual J, Zhang N, Kemerer M, Maeda T, Palczewski K, Von Lintig J. STRA6 is critical for cellular vitamin A uptake and homeostasis. Hum Mol Genet. 2014;23(20):5402–17.
35. Noorian S, Kwaan MR, Jaffe N, Yaceczko SD, Chau LW. Perioperative nutrition for gastrointestinal surgery: on the cutting edge. Nutr Clin Pract. 2023;38(3):539–56.
36. Zalesin KC, Miller WM, Franklin B, Mudugal D, Rao Buragadda A, Boura J, Nori-Janosz K, Chengelis DL, Krause KR, McCullough PA. Vitamin a deficiency after gastric bypass surgery: an underreported postoperative complication. J Obes. 2011. https://doi.org/10.1155/2011/760695.
37. D'Ambrosio DN, Clugston RD, Blaner WS. Vitamin A metabolism: an update. Nutrients. 2011;3(1):63–103.
38. Sarkar H, Moosajee M. Retinol dehydrogenase 12 (RDH12): Role in vision, retinal disease and future perspectives. Exp Eye Res. 2019;188: 107793.
39. Klamt F, Dal-Pizzol F, Gelain DP, Dalmolin RS, Birnfeld de Oliveira R, Bastiani M, Horn F, Fonseca Moreira JC. Vitamin A treatment induces apoptosis through an oxidant-dependent activation of the mitochondrial pathway. Cell Biol Int. 2008;32(1):100–6.
40. Takahashi N. Inhibitory effects of vitamin A and its derivatives on cancer cell growth not mediated by retinoic acid receptors. Biol Pharm Bull. 2022;45(9):1213–24.
41. Al Tanoury Z, Piskunov A, Rochette-Egly C. Vitamin A and retinoid signaling: genomic and nongenomic effects. J Lipid Res. 2013;54(7):1761–75.
42. Balmer JE, Blomhoff R. Gene expression regulation by retinoic acid. J Lipid Res. 2002;43(11):1773–808.
43. Sun L, Zheng M, Gao Y, Brigstock DR, Gao R. Retinoic acid signaling pathway in pancreatic stellate cells: Insight into the anti-fibrotic effect and mechanism. Eur J Pharmacol. 2024;967: 176374.
44. Pan J, Kao YL, Joshi S, Jeetendran S, Dipette D, Singh US. Activation of Rac1 by phosphatidylinositol 3-kinase in vivo: role in activation of mitogen-activated protein kinase (MAPK) pathways and retinoic acid-induced neuronal differentiation of SH-SY5Y cells. J Neurochem. 2005;93(3):571–83.
45. Masia S, Alvarez S, de Lera AR, Barettino D. Rapid, nongenomic actions of retinoic acid on phosphatidylinositol-3-kinase signaling pathway mediated by the retinoic acid receptor. Mol Endocrinol. 2007;21(10):2391–402.
46. Cheung YT, Lau WK, Yu MS, Lai CS, Yeung SC, So KF, Chang RC. Effects of all-trans-retinoic acid on human SH-SY5Y neuroblastoma as in vitro model in neurotoxicity research. Neurotoxicology. 2009;30(1):127–35.
47. Berry DC, O'Byrne SM, Vreeland AC, Blaner WS, Noy N. Cross talk between signaling and vitamin A transport by the retinol-binding protein receptor STRA6. Mol Cell Biol. 2012;32(15):3164–75.
48. Liang C, Qiao G, Liu Y, Tian L, Hui N, Li J, Ma Y, Li H, Zhao Q, Cao W, et al. Overview of all-trans-retinoic acid (ATRA) and its analogues: structures, activities, and mechanisms in acute promyelocytic leukaemia. Eur J Med Chem. 2021;220: 113451.
49. Yilmaz M, Kantarjian H, Ravandi F. Acute promyelocytic leukemia current treatment algorithms. Blood Cancer J. 2021;11(6):123.
50. Reay WR, Kiltschewskij DJ, Di Biase MA, Gerring ZF, Kundu K, Surendran P, Greco LA, Clarke ED, Collins CE, Mondul AM, et al. Genetic influences on circulating retinol and its relationship to human health. Nat Commun. 2024;15(1):1490.
51. Hada M, Mondul AM, Weinstein SJ, Albanes D. Serum retinol and risk of overall and site-specific cancer in the ATBC study. Am J Epidemiol. 2020;189(6):532–42.
52. Loh WQ, Yin X, Kishida R, Chia SE, Ong CN, Seow WJ. Association between vitamin A and E forms and prostate cancer risk in the Singapore prostate cancer study. Nutrients. 2023. https://doi.org/10.3390/nu15122677.

53. Xie L, Song Y, Lin T, Guo H, Wang B, Tang G, Liu C, Huang W, Yang Y, Ling W, et al. Association of plasma retinol levels with incident cancer risk in Chinese hypertensive adults: a nested case-control study. Br J Nutr. 2019;122(3):293–300.
54. Bui AQ, Gunathilake M, Lee J, Oh JH, Chang HJ, Sohn DK, Shin A, Kim J. Interaction between retinol intake and ISX rs5755368 polymorphism in colorectal cancer risk: a case-control study in a Korean population. Sci Rep. 2023;13(1):10187.
55. Chen QH, Wu BK, Pan D, Sang LX, Chang B. Beta-carotene and its protective effect on gastric cancer. World J Clin Cases. 2021;9(23):6591–607.
56. Han W, Zhang W, Ren X. Not all carotenoids can reduce the risk of gastric cancer: a systematic review with meta-analysis. BMC Gastroenterol. 2024;24(1):51.
57. Comstock GW, Bush TL, Helzlsouer K. Serum retinol, beta-carotene, vitamin E, and selenium as related to subsequent cancer of specific sites. Am J Epidemiol. 1992;135(2):115–21.
58. Mondul AM, Watters JL, Mannisto S, Weinstein SJ, Snyder K, Virtamo J, Albanes D. Serum retinol and risk of prostate cancer. Am J Epidemiol. 2011;173(7):813–21.
59. Nash SH, Till C, Song X, Lucia MS, Parnes HL, Thompson IM Jr, Lippman SM, Platz EA, Schenk J. Serum retinol and carotenoid concentrations and prostate cancer risk: results from the prostate cancer prevention trial. Cancer Epidemiol Biomarkers Prev. 2015;24(10):1507–15.
60. Sanz MA, Fenaux P, Tallman MS, Estey EH, Lowenberg B, Naoe T, Lengfelder E, Dohner H, Burnett AK, Chen SJ, et al. Management of acute promyelocytic leukemia: updated recommendations from an expert panel of the European LeukemiaNet. Blood. 2019;133(15):1630–43.
61. Dearden CE, Johnson R, Pettengell R, Devereux S, Cwynarski K, Whittaker S, McMillan A, British Committee for Standards in H. Guidelines for the management of mature T-cell and NK-cell neoplasms (excluding cutaneous T-cell lymphoma). Br J Haematol. 2011;153(4):451–85.
62. Klaassen I, Brakenhoff RH, Smeets SJ, Snow GB, Braakhuis BJ. Metabolism and growth inhibition of four retinoids in head and neck squamous normal and malignant cells. Br J Cancer. 2001;85(4):630–5.
63. Heliovaara MK, Remitz A, Reitamo S, Teppo AM, Karonen SL, Ebeling P. 13-cis-Retinoic acid therapy induces insulin resistance, regulates inflammatory parameters, and paradoxically increases serum adiponectin concentration. Metabolism. 2007;56(6):786–91.
64. Zapata-Gonzalez F, Rueda F, Petriz J, Domingo P, Villarroya F, de Madariaga A, Domingo JC. 9-cis-Retinoic acid (9cRA), a retinoid X receptor (RXR) ligand, exerts immunosuppressive effects on dendritic cells by RXR-dependent activation: inhibition of peroxisome proliferator-activated receptor gamma blocks some of the 9cRA activities, and precludes them to mature phenotype development. J Immunol. 2007;178(10):6130–9.
65. Tatebe H, Shimizu M, Shirakami Y, Tsurumi H, Moriwaki H. Synergistic growth inhibition by 9-cis-retinoic acid plus trastuzumab in human hepatocellular carcinoma cells. Clin Cancer Res. 2008;14(9):2806–12.
66. McCormick DL, Rao KV, Steele VE, Lubet RA, Kelloff GJ, Bosland MC. Chemoprevention of rat prostate carcinogenesis by 9-cis-retinoic acid. Cancer Res. 1999;59(3):521–4.
67. Kamstrup M, Gniadecki R. Bexarotene monotherapy for epidermotropic CD8+ CTCL. Dermatol Clin. 2008;26(Suppl 1):45–7.
68. Berg SE, Downs LH, Torigian DA, Chong EA, Tsai DE, Wasik MA, Schuster SJ. Successful treatment of relapsed lymphomatoid granulomatosis with bexarotene. Cancer Biol Ther. 2008;7(10):1544–6.
69. Carratu MR, Marasco C, Mangialardi G, Vacca A. Retinoids: novel immunomodulators and tumour-suppressive agents? Br J Pharmacol. 2012;167(3):483–92.
70. Dillon S, Agrawal S, Banerjee K, Letterio J, Denning TL, Oswald-Richter K, Kasprowicz DJ, Kellar K, Pare J, van Dyke T, et al. Yeast zymosan, a stimulus for TLR2 and dectin-1, induces regulatory antigen-presenting cells and immunological tolerance. J Clin Invest. 2006;116(4):916–28.
71. Veldhoen M, Hirota K, Westendorf AM, Buer J, Dumoutier L, Renauld JC, Stockinger B. The aryl hydrocarbon receptor links TH17-cell-mediated autoimmunity to environmental toxins. Nature. 2008;453(7191):106–9.
72. Wang Z, Cao Y, D'Urso CM, Ferrone S. Differential susceptibility of cultured human melanoma cell lines to enhancement by retinoic acid of intercellular adhesion molecule 1 expression. Cancer Res. 1992;52(17):4766–72.
73. Vertuani S, Dubrovska E, Levitsky V, Jager MJ, Kiessling R, Levitskaya J. Retinoic acid elicits cytostatic, cytotoxic and immunomodulatory effects on uveal melanoma cells. Cancer Immunol Immunother. 2007;56(2):193–204.
74. Olson DJ, Luke JJ. Myeloid maturity: ATRA to enhance anti-PD-1? Clin Cancer Res. 2023;29(7):1167–9.
75. Peng Z, Wang J, Guo J, Li X, Wang S, Xie Y, Jiang H, Wang Y, Wang M, Hu M, et al. All-trans retinoic acid improves NSD2-mediated RARα phase separation and efficacy of anti-CD38 CAR T-cell therapy in multiple myeloma. J Immunother Cancer. 2023. https://doi.org/10.1136/jitc-2022-006325.
76. Carazo A, Macakova K, Matousova K, Krcmova LK, Protti M, Mladenka P. Vitamin A update: forms, sources, kinetics, detection, function, deficiency, therapeutic use and toxicity. Nutrients. 2021. https://doi.org/10.3390/nu13051703.
77. Farrington K, Miller P, Varghese Z, Baillod RA, Moorhead JF. Vitamin A toxicity and hypercalcaemia in chronic renal failure. Br Med J (Clin Res Ed). 1981;282(6281):1999–2002.
78. Hathcock JN, Hattan DG, Jenkins MY, McDonald JT, Sundaresan PR, Wilkening VL. Evaluation of vitamin A toxicity. Am J Clin Nutr. 1990;52(2):183–202.
79. Maurya VK, Shakya A, Bashir K, Kushwaha SC, McClements DJ. Vitamin A fortification: recent advances in encapsulation technologies. Compr Rev Food Sci Food Saf. 2022;21(3):2772–819.
80. Geng XQ, Ma A, He JZ, Wang L, Jia YL, Shao GY, Li M, Zhou H, Lin SQ, Ran JH, et al. Ganoderic acid hinders renal fibrosis via suppressing the TGF-beta/Smad and MAPK signaling pathways. Acta Pharmacol Sin. 2020;41(5):670–7.
81. Goenka A, Khan F, Verma B, Sinha P, Dmello CC, Jogalekar MP, Gangadaran P, Ahn BC. Tumor microenvironment signaling and therapeutics in cancer progression. Cancer Commun (Lond). 2023;43(5):525–61.
82. Peng D, Fu M, Wang M, Wei Y, Wei X. Targeting TGF-beta signal transduction for fibrosis and cancer therapy. Mol Cancer. 2022;21(1):104.
83. Li K, Huang Z, Xie G, et al. Transcriptomic insights into UTUC: role of inflammatory fibrosis and potential for personalized treatment. J Transl Med. 2024;22:24. https://doi.org/10.1186/s12967-023-04815-y.
84. Jablonska-Trypuc A, Matejczyk M, Rosochacki S. Matrix metalloproteinases (MMPs), the main extracellular matrix (ECM) enzymes in collagen degradation, as a target for anticancer drugs. J Enzyme Inhib Med Chem. 2016;31(sup1):177–83.

85. Horn LA, Chariou PL, Gameiro SR, Qin H, Iida M, Fousek K, Meyer TJ, Cam M, Flies D, Langermann S, et al. Remodeling the tumor microenvironment via blockade of LAIR-1 and TGF-beta signaling enables PD-L1-mediated tumor eradication. J Clin Invest. 2022. https://doi.org/10.1172/JCI155148.
86. He L, Kang Q, Chan KI, Zhang Y, Zhong Z, Tan W. The immunomodulatory role of matrix metalloproteinases in colitis-associated cancer. Front Immunol. 2022;13:1093990.
87. Marimastat. BB 2516, TA 2516. Drugs R D 2003;4(3):198–203.
88. Huang W, Zhang L, Yang M, Wu X, Wang X, Huang W, Yuan L, Pan H, Wang Y, Wang Z, et al. Cancer-associated fibroblasts promote the survival of irradiated nasopharyngeal carcinoma cells via the NF-kappaB pathway. J Exp Clin Cancer Res. 2021;40(1):87.
89. Desgrosellier JS, Cheresh DA. Integrins in cancer: biological implications and therapeutic opportunities. Nat Rev Cancer. 2010;10(1):9–22.
90. Esteban-Pretel G, Marín MP, Renau-Piqueras J, Sado Y, Barber T, Timoneda J. Vitamin A deficiency disturbs collagen IV and laminin composition and decreases matrix metalloproteinase concentrations in rat lung. Partial reversibility by retinoic acid. J Nutr Biochem. 2013;24(1):137–45.
91. Axel DI, Frigge A, Dittmann J, Runge H, Spyridopoulos I, Riessen R, Viebahn R, Karsch KR. All-trans retinoic acid regulates proliferation, migration, differentiation, and extracellular matrix turnover of human arterial smooth muscle cells. Cardiovasc Res. 2001;49(4):851–62.
92. Park EY, Wilder ET, Lane MA. Retinol inhibits the invasion of retinoic acid-resistant colon cancer cells in vitro and decreases matrix metalloproteinase mRNA, protein, and activity levels. Nutr Cancer. 2007;57(1):66–77.
93. Li X, Zhang L, Yin X, Gao Z, Zhang H, Liu X, Pan X, Li N, Yu Z. Retinoic acid remodels extracellular matrix (ECM) of cultured human fetal palate mesenchymal cells (hFPMCs) through down-regulation of TGF-beta/Smad signaling. Toxicol Lett. 2014;225(2):208–15.
94. Comptour A, Rouzaire M, Belville C, Bonnin N, Daniel E, Chiambaretta F, Blanchon L, Sapin V. Lysyl oxidase-like 4 involvement in retinoic acid epithelial wound healing. Sci Rep. 2016;6:32688.
95. Korzekwa AJ, Kononiuk A, Kordan W, Orzolek A. Retinoic acid alters metalloproteinase action in red deer antler stem cells. PLoS ONE. 2023;18(7): e0287782.
96. Dheen ST, Jun Y, Yan Z, Tay SS, Ling EA. Retinoic acid inhibits expression of TNF-alpha and iNOS in activated rat microglia. Glia. 2005;50(1):21–31.
97. Pendaries V, Verrecchia F, Michel S, Mauviel A. Retinoic acid receptors interfere with the TGF-beta/Smad signaling pathway in a ligand-specific manner. Oncogene. 2003;22(50):8212–20.
98. Cheng YH, Chiang EI, Syu JN, Chao CY, Lin HY, Lin CC, Yang MD, Tsai SY, Tang FY. Treatment of 13-cis retinoic acid and 1,25-dihydroxyvitamin D3 inhibits TNF-alpha-mediated expression of MMP-9 protein and cell invasion through the suppression of JNK pathway and microRNA 221 in human pancreatic adenocarcinoma cancer cells. PLoS ONE. 2021;16(3): e0247550.
99. Kashif M, Yao H, Schmidt S, Chen X, Truong M, Tuksammel E, Liu Y, Bergo MO. ROS-lowering doses of vitamins C and A accelerate malignant melanoma metastasis. Redox Biol. 2023;60: 102619.
100. Davies A, Zoubeidi A, Beltran H, Selth LA. The transcriptional and epigenetic landscape of cancer cell lineage plasticity. Cancer Discov. 2023;13(8):1771–88.
101. Lin S, Margueron R, Charafe-Jauffret E, Ginestier C. Disruption of lineage integrity as a precursor to breast tumor initiation. Trends Cell Biol. 2023;33(10):887–97.
102. Perez LM, Venugopal SV, Martin AS, Freedland SJ, Di Vizio D, Freeman MR. Mechanisms governing lineage plasticity and metabolic reprogramming in cancer. Trends Cancer. 2024;10(11):1009–22.
103. Roy AM, Iyer R, Chakraborty S. The extracellular matrix in hepatocellular carcinoma: mechanisms and therapeutic vulnerability. Cell Rep Med. 2023;4(9): 101170.
104. Klingberg F, Hinz B, White ES. The myofibroblast matrix: implications for tissue repair and fibrosis. J Pathol. 2013;229(2):298–309.
105. Akkız H, Gieseler RK, Canbay A. Liver fibrosis: from basic science towards clinical progress, focusing on the central role of hepatic stellate cells. Int J Mol Sci. 2024. https://doi.org/10.3390/ijms25147873.
106. Hsu SL, Cheng CC, Shi YR, Chiang CW. Proteolysis of integrin alpha5 and beta1 subunits involved in retinoic acid-induced apoptosis in human hepatoma Hep3B cells. Cancer Lett. 2001;167(2):193–204.
107. Chronopoulos A, Robinson B, Sarper M, Cortes E, Auernheimer V, Lachowski D, Attwood S, Garcia R, Ghassemi S, Fabry B, et al. ATRA mechanically reprograms pancreatic stellate cells to suppress matrix remodelling and inhibit cancer cell invasion. Nat Commun. 2016;7:12630.
108. Zhang H, Yue X, Chen Z, Liu C, Wu W, Zhang N, Liu Z, Yang L, Jiang Q, Cheng Q, et al. Define cancer-associated fibroblasts (CAFs) in the tumor microenvironment: new opportunities in cancer immunotherapy and advances in clinical trials. Mol Cancer. 2023;22(1):159.
109. Wang D, Pei P, Shea FF, Bissonnette C, Nieto K, Din C, Liu Y, Schwendeman SP, Lin YX, Spinney R, et al. Fenretinide combines perturbation of signaling kinases, cell-extracellular matrix interactions and matrix metalloproteinase activation to inhibit invasion in oral squamous cell carcinoma cells. Carcinogenesis. 2022;43(9):851–64.
110. Shoari A. Potential of MMP-2 and MMP-9 gelatinase blockade as a therapeutic strategy in fibrosarcoma treatment: a decadal review. Targets. 2024;2(2):104–25.