Supplementary Information (SI) for Journal of Materials Chemistry B.

Supplemental Figures:

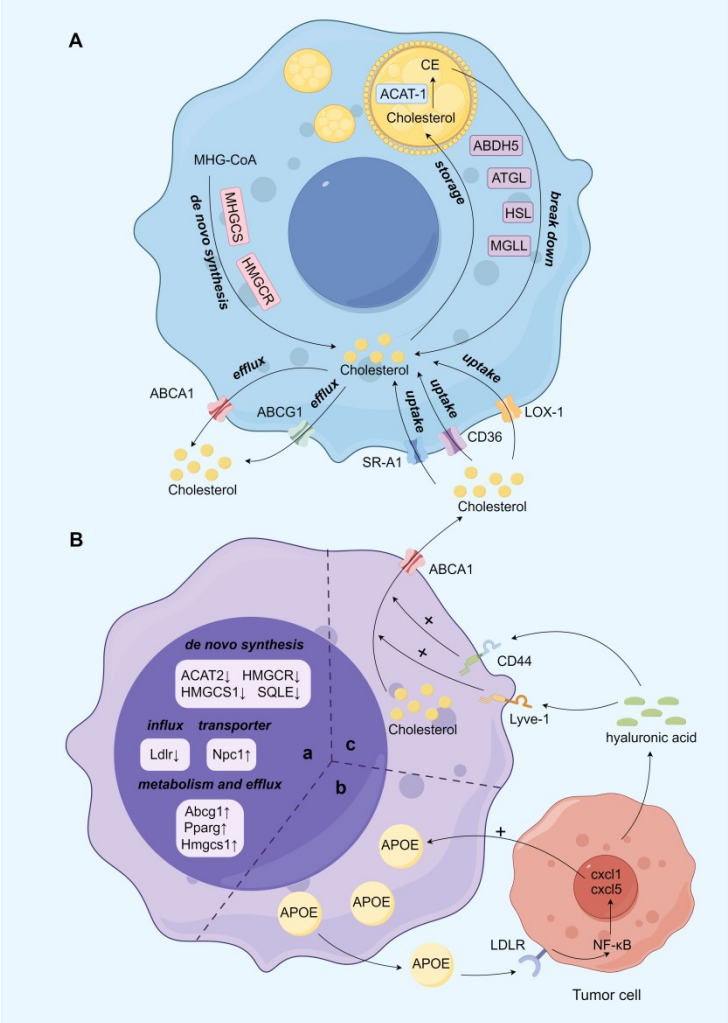

Figure S1. Cholesterol metabolism in Macrophages versus TAMs. A: Normal macrophages perform cholesterol metabolism through uptake, de novo synthesis, storage and efflux. B: **(a)** TAMs showed reduced expression of genes involved in cholesterol de novo synthesis and cholesterol influx, whereas the expression of genes involved in cholesterol metabolism, efflux, and cholesterol transport was upregulated. **(b)** TAMs interact with tumor cells to elevate ApoE expression, leading to increased cholesterol efflux. **(c)** The tumor cell product hyaluronic acid acts on TAMs to facilitate cholesterol efflux.

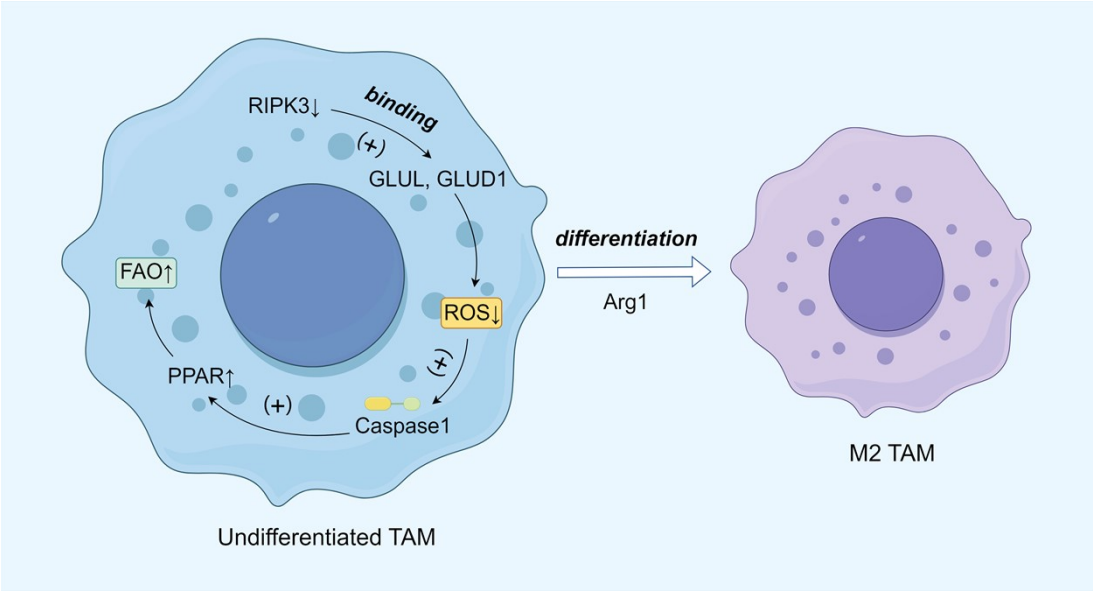

Figure S2. Macrophages mediated by RIPK3 deficiency are susceptible to differentiation towards the M2 phenotype. RIPK3 deficiency reduces ROS production, which subsequently leads to a reduction in Caspase-1-mediated cleavage of PPAR, and elevated levels of PPAR regulate the gene expression of molecules encoding molecules used for FAO, such as inducing the expression of Arg1, which predisposes macrophages to differentiate toward the M2 phenotype.

Supplemental Tables:

Table 1. The senescent cells produced SASPs.

SASPs	Senescent cells	Role in tumor immunity	Ref.
IL-6	Osteoblast		[1]
CCL5	Melanocyte	Promoting tumor immunity	[2]
CXCL14	Hepatocyte		[3]
VEGF	Pancreatic ductal cell		[4]
IL-6, IFN-γ	Hepatic stellate cell		[5-6]
IL-1β	Hepatic stellate cell		[7]
CCL2	Hepatocyte		[8]
MMPs	Fibroblast		[9]
CXCL1 CXCL2	Prostate epithelial cell	Suppressing tumor immunity	[10]
CXCL12	Thyroid follicular cell		[11]
IL-6	Melanocyte		[12]
IL-1β	Bronchial cell		[13]

Table S2. Drugs in clinical trials targeting abnormal cholesterol metabolism in tumor-associated macrophages.

Active Ingredient	Tumor type	Target Gene	Interventions	Locations	Clinical Status	Ref.
Atorvastatin	Prostate cancer	HMG-CoA	Atorvastatin	Finland	Phase 2	[14]
Statin	Solid tumors	HMG-CoA	Statin	Egypt	Phase 1/2	[15]
Oncolytic Virus	Triple-negative breast cancer	ApoA1	Oncolytic virus (ADV-ApoA1) injection	China	Not Applicable	[16]
Fenofibrate	Multiple myeloma	PPARα	Fenofibrate	United States	Phase 2	—
GSK5733584	Advanced solid tumor	B7-H4	Intravenous injection of GSK5733584	Japan	Phase 1	—
Cholesterol-fus1	Lung cancer	fus1	DOTAP：Chol-fus1	United States	Phase 1	[14]
TAS-117 and TAS-120	Advanced solid tumors	Akt and FGFR	TAS-117 combined with TAS-120	Japan	Phase 1/2	—

Table S3. Nanomaterials in clinical trials targeting abnormal cholesterol metabolism.

Vehicle Type	Active Ingredient	Specific Materials	Type of disease	Target	Interventions	Locations	Clinical Status	Ref.
Liposome	Methotrexate	LDE	COVID-19	DHFR	Methotrexate-LDE	Brazil	Phase 1/2	[17]
Liposome	Paclitaxel	LDE	Stable coronary disease	tubulin	LDE-Paclitaxel	Brazil	Phase 2/3	[18]
Liposome	Methotrexate	LDE	Stable coronary disease	DHFR	Methotrexate-LDE	Brazil	Phase 2/3	[19]
Liposome	Phospholipovit	Phospholipids nanoemulsion	atherosclerosis	HDL	Phospholipovit	Russian Federation	Phase 2/3	—
Complex	IL-12 DNA Plasmid Vector GEN-1 and Pegylated Liposomal Doxorubicin Hydrochlori	PEG-PEI-cholesterol Lipopolymer	Ovarian epithelial, fallopian tube and primary peritoneal cancer	EGFR	PEG-PEI-cholesterol Lipopolymer-encased IL-12 DNA Plasmid Vector GEN-1	United States	Phase 1	—

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Table S4. Key studies on cholesterol metabolism abnormalities in TAMs and tumor immune suppression

Key Finding	Mechanism	Impact on Tumor Immunity	Ref.
Tumor cells promote cholesterol efflux from TAMs, depleting membrane cholesterol.	Depleted cholesterol activates PI3K-AKT-mTORC2, enhancing IL-4-induced M2 polarization.	Promotes immunosuppressive TME; reduces $CD8^+$ T cell activity.	20
NPC1 upregulation in TAMs reduces intracellular cholesterol levels.	Enhanced cholesterol export via NPC1 disrupts lipid raft signaling.	Impairs antigen presentation; dampens anti-tumor immunity.	21
CH25H/25HC axis in TAMs depletes arginine via Arg1 upregulation.	25HC inhibits T cell proliferation by reducing arginine availability.	Suppresses cytotoxic T cell responses; facilitates immune escape.	22

Low cholesterol in TME induces CD8+ T cell dysfunction and autophagy.	Cholesterol deficiency downregulates hypoxia-induced anti-tumor pathways.	Reduces T cell cytotoxicity and survival.	23
Impaired cholesterol efflux in prostate cancer TAMs reduces androgen synthesis in tumor cells.	Low cholesterol limits androgen receptor activation in cancer cells.	Slows tumor progression but sustains immunosuppressive TME.	24

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