Trends in Immunology

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Review

NF-κB: blending metabolism, immunity, and inflammation

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The procurement and management of nutrients and ability to fight infections are fundamental requirements for survival. These defense responses are bioenergetically costly, requiring the immune system to balance protection against pathogens with the need to maintain metabolic homeostasis. NF-κB transcription factors are central regulators of immunity and inflammation. Over the last two decades, these factors have emerged as a pivotal node coordinating the immune and metabolic systems in physiology and the etiopathogenesis of major threats to human health, including cancer, autoimmunity, chronic inflammation, and others. In this review, we discuss recent advances in understanding how NF-κB-dependent metabolic programs control inflammation, metabolism, and immunity and how improved knowledge of them may lead to better diagnostics and therapeutics for widespread human diseases.

Cross-coordination of the immune and metabolic systems: adding fuel to the fire

NF-κB transcription factors have historically been known for their central role in coordinating immune and inflammation responses (Box 1) [1]. Early seminal studies using either liver-specific IκBα kinase (IKK)β conditional knockout and transgenic mouse models demonstrated that IκBα kinase IKK/NF-κB signaling is also a major driver of chronic low-grade inflammation, often referred to as 'metabolic inflammation' or 'meta-inflammation', that underpins metabolic diseases, including type 2 diabetes and insulin resistance [2,3]. Later studies in mice reported that IKK/NF-κB signaling drives tissue-specific inflammation induced by nutritional excess, contributing to obesity and energy imbalance [4,5]. Subsequently, a flurry of discoveries reported an intimate connection between the mammalian IKK/NF-κB system and metabolism (Table 1) that extends well beyond meta-inflammation, exposing how the NF-κB transcriptional machinery is hardwired to a diversity of tissue- and context-specific metabolic programs, implicated in oncogenesis, immunoregulation, energy homeostasis, aging, and stem cell renewal[i] [6–8].

The intertwined involvement of NF-κB in defense responses and metabolism reflects the close integration and coevolution of nutrient- and pathogen-sensing and management systems [6,9]. In this review, we discuss the latest advances on how NF-κB regulates mammalian metabolic networks that control B cell differentiation and function, cancer, and inflammation. We consider how this knowledge might be exploited to develop better treatments and diagnostics to improve the management of human diseases and explore new frontiers for future investigation. Topics on the previously established functions of NF-κB in pro-/anti-inflammatory lipid metabolism, redox homeostasis, and systemic metabolic imbalances, have been extensively discussed elsewhere [7,9–13].

Metabolic reprogramming of germinal center (GC) B cells by NF-κB

Upon activation by T-dependent antigens, B cells undergo **affinity maturation** (see Glossary) within GCs in secondary lymphoid tissues to generate plasma cells (PCs) that produce high-

Significance

NF-κB is central to immune and inflammatory responses but a long-standing question is if and how NF-κB integrates host responses against injury and microbial pathogens by reprogramming cell metabolism. A recent flurry of studies has now partially resolved this conundrum, underscoring how the NF-κB transcriptional machinery is inherently hardwired to the metabolic programs that govern immune regulation, energy homeostasis, and oncogenesis.

Highlights

The NF-κB subunit Rel is a major regulator of energy metabolism and biosynthetic pathways in germinal center B cells and human B cell lymphomas, and treatment with small-molecules REL inhibitors can effectively counteract lymphomagenesis in certain preclinical animal models.

NF-κB-regulated metabolic enzymes such as 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase isoform (3PFKFB3), glutamate dehydrogenase 1 (GDH1), and carboxylesterase 1 (CES1), are pivotal effectors of NF-κB-dependent metabolic adaptation of cancer cells to nutrient deprivation and, as such, represent potentially actionable therapeutic targets in oncology.

Rel/REL mediates an innate immune checkpoint that governs the generation, function, and metabolism of myeloid-derived suppressor cells (MDSCs) and can promote oncogenesis by suppressing antitumor immune responses. REL inhibition might enhance the therapeutic efficacy of current immune checkpoint immunotherapies.

The activation of NF-κB in cancer-associated fibroblasts in response to tumor-secreted lactate can promote

Box 1. NF-κB signaling pathway

In mammals, the NF-κB transcription factor family consists of five members named p65 (RELA), RELB, REL, NF-κB1 (p105/p50), and NF-κB2 (p/100/p52) [80]. Among these members, NF-κB1 and NF-κB2 are synthesized as preforms, p105 and p100, which are then processed to p50 and p52, respectively, two transcriptional repressors that lack the transactivation domain [80,81]. All five members form homo- or heterodimers, among which p65/p50 is the most common one [80]. All NF-κB factors have a conserved Rel homology domain (RHD) of 300 amino acids in the N-terminal region, responsible for dimerization, binding to specific DNA regions, nuclear translocation, and interaction with IκB regulatory proteins. In the canonical NF-κB pathway, which is responsible for the activation of NF-κB1 p50, p65, and REL, NF-κB dimers are sequestered in the cytoplasm by IκB proteins (IκBα, IκBβ, IκBε, IκBζ, IκBκ, and Bcl-3). Upon activation by: (i) inflammatory cytokines, including necrosis factor-α (TNF-α) and interleukin 1β (IL-1β), which bind to their receptors TNF-R1 and IL-βR; (ii) pathogen-associated molecular patterns (PAMPs) and molecules released by host cells that bind toll-like receptors (TLRs); and (iii) stress signals such as genotoxic stress [81,82], the multi-subunit IκB kinase complex (IKK), containing two catalytic subunits IKKα (IKK1) and IKKβ (IKK2) and at least one noncatalytic regulatory subunit, NF-κB essential modulator (NEMO; also called IKKγ), phosphorylates IκB inhibitors, which, in turn, are polyubiquitinated and subsequently degraded by the 26S proteasome. Consequently, p65/p50 complexes are released and free to translocate to the nucleus. The noncanonical pathway leads to the processing of p100 and is activated in response to lymphotoxin β (LTβ), CD40 ligand (CD40L), B cell activating factor (BAFF), receptor activator of NF-κB ligand (RANKL), TNF-related weak inducer of apoptosis (TWEAK), and tumor necrosis factor superfamily member 14 (TNFSF14; also known as LIGHT) [82]. The first step of activation is the stabilization of NF-κB-inducing kinase (NIK), which in turn phosphorylates IKKα, leading to the p100 processing to p52 and the nuclear translocation of p52 and RELB [81].

affinity antibodies and memory B cells (MBCs) (Box 2) [14]; these cells induce secondary immune responses upon re-encountering related antigens. **Dark zone (DZ) B cells** proliferate at a faster rate than any other mouse cells, with a cell cycle time of 5 to 12 h and, as such, must confront the heightened metabolic demands of rapid cell division. Conversely, light zone (LZ) B cells must cope with a hypoxic microenvironment.

Early studies showed that the NF-κB Rel subunit is activated in a subset of LZ B cells, where it controls a metabolic program that promotes cell growth and proliferation by generating energy and reducing equivalents and biosynthetic intermediates to increase biomass in dividing cells [15] (Figure 1). Accordingly, GC B cell-specific Rel deletion in mice (*Rel*$^{fl/fl}$;*Cy1*-Cre) resulted in the collapse of established GCs immediately upon formation of discernible DZs and LZs, due to a failure to upregulate genes that govern metabolism and cell cycle entry or progression [15]. Among the genes most downregulated by Rel loss in GC B cells were those encoding phosphofructokinase (*Pfkm*), the rate-limiting enzyme in **glycolysis**, phosphoglycerate dehydrogenase (*Phgdh*), which shunts glycolysis-derived carbons toward amino acid metabolism, solute carrier family 7 member 6 (*Slc7a6*), which transports glutamine and other amino acids across the plasma membrane to fuel **anabolic reactions**, and several enzymes involved in **fatty acid oxidation (FAO)**, a major source of energy and NADPH (Figure 1). **Oxidative phosphorylation (OXPHOS)** and glycolytic flux were correspondingly reduced in Rel-deficient compared with wild type splenic B cells isolated from *Rel*$^{fl/fl}$;*Cy1*-Cre and *CD19*-Cre control mice upon mitogenic stimulation, resulting in diminished **oxygen consumption rate (OCR)**, **extracellular acidification rate (ECAR)**, and ATP production [15]. Based on similarities with the effects of antibody-mediated CD40-CD40L inhibition, it was suggested that, upon CD40-dependent activation, Rel licenses a subset of LZ B cells for DZ re-entry to undergo further rounds of proliferation, thus maintaining the GC reaction [15]. This, however, was not experimentally demonstrated. The recent characterization of the LZ subpopulations representing pre-plasmablasts (pre-PBs), MBC precursors, and DZ re-entrants [16] now allows this hypothesis to be tested, determining whether *Rel* loss selectively impairs metabolism of recirculating LZ B cells. Of note, Myc denotes the subset of positively selected B cells in the LZ and, akin to the *Rel* knockout, its loss was shown to impair the maintenance, but not formation, of GCs. This was demonstrated when doxycycline-inducible expression of the selective Myc antagonist, Omomyc, in TRE-Omomyc rtTA-actin transgenic mice led to a rapid collapse of fully developed GCs 10 days post-immunization, with a reduction in numbers of both centrocytes and

therapy resistance in lung cancer cells by increasing the secretion of hepatocyte growth factor (HGF).

NF-κB is a major sensor of metabolic imbalances that result in inflammasome activation.

Understanding how NF-κB-dependent metabolic regulation governs physiology and disease states opens new opportunities for therapeutic intervention in cancer and immune-mediated diseases.

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Table 1. NF-κB metabolic network

Metabolic factors regulating NF-κB				
Gene	Symbol	Biological context	Species[a]	Refs
Glutamate dehydrogenase 1	GDH1	Glutamine metabolism	HS/mm	[32]
Hexokinase 1	Hk1	Glucose metabolism	mm	[50]
Glyceraldehyde-3-phosphate dehydrogenase	Gapdh	Glucose metabolism	mm	[51]
Sterol regulatory element binding transcription factor 2	SCAP/SREBP2	Transcription factor that controls cholesterol homeostasis	HS	[57]
Sirtuin 2	SIRT2	Deacetylase	HS/mm	[61]
TP53 induced glycolysis regulatory phosphatase	TIGAR	Regulation of carbon flux through the glycolytic and pentose phosphate pathways	HS/mm	[64]
Pyruvate kinase M2	PKM2	Glucose metabolism	HS	[65]
Metabolites	Abbreviations	Biological context	Species	Refs
Alpha-ketoglutarate	αKG	TCA cycle	HS/mm	[32]
Lactate	LAC	Glucose metabolism	HS/mm	[44]
β-Glucan	βG	Polysaccharide of fungal cell wall	HS	[53]
Succinate	SUCC	TCA cycle	RN	[54]
β-Hydroxybutyrate	BHB	TCA cycle	HS/mm	[55]
Itaconate	IT	TCA cycle	HS/mm	[56]
Polyunsaturated fatty acids	PUFAs	Fatty acid metabolism	mm	[58]
Saturated fatty acids	SFAs	Fatty acid metabolism	HS/mm	[59]
Phosphatidylinositol/ phosphatidylinositol (PI) 4-phosphate	PI/PTDINS4P	Second messenger	HS/mm	[60]
NF-κB-regulated metabolic genes				
Gene	Symbol	Biological context	Species	Refs
Solute carrier family 7 member 6	*Slc7a6*	Basic amino acid transmembrane transport and ornithine transport	mm	[15]
Phosphofructokinase, muscle	*Pfkm*	Carbohydrate metabolism	mm	[15]
Phosphoglycerate dehydrogenase	*Phgdh*	L-Serine synthesis	mm	[15]
Fatty acid desaturase 2	*Fads2*	Unsaturation of fatty acids	mm	[15]
Aspartylglucosaminidase	*Aga*	Catabolism of *N*-linked oligosaccharides of glycoproteins	mm	[15]
Glutamic-pyruvic transaminase 2	*Gpt2*	Gluconeogenesis and amino acid metabolism	mm	[15]
Acyl-CoA synthetase short chain family member 2	*Acss2*	Lipid biosynthesis	mm	[15]
Acyl-CoA synthetase long chain family member 4	*Acsl4*	Lipid biosynthesis	mm	[15]
Acyl-CoA dehydrogenase family member 9	*Acad9*	Fatty acid metabolism	mm	[15]
Phospholipase A and acyltransferase 3	*Plaat3 (Pla2g16)*	*N*-acylphosphatidylethanolamine metabolic process	mm	[15]
MYC proto-oncogene	*Myc*	Cell cycle progression, apoptosis, and cellular transformation	mm	[19]

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Glossary

Adoptive cell transfer: type of immunotherapy in which a cancer patient's own T cells with antitumor activity are expanded *in vitro* and reinfused into the patient to help immune cells fight cancer.
Affinity maturation: process where B cells produce antibodies with successively greater affinity for antigen upon its repeated presentation by follicular dendritic cells.
Anabolic reactions: use of energy to build complex molecules from smaller units.
Anaplerosis: process of replenishment of depleted tricarboxylic acid cycle intermediates.
Cryopyrin-associated periodic syndrome (CAPS): group of rare hereditary autoinflammatory disorders associated with defects in the protein NLRP3/cryopyrin.
Dark zone (DZ) B cells: localized in the dark zone of the germinal center; undergo expansion and somatic mutation of their antibody variable region genes.
Extracellular acidification rate (ECAR): rate at which cells acidify the extracellular medium due to the activation of glycolysis.
Fatty acid desaturation: the formation of a carbon–carbon double bond into a fatty acid chain is catalyzed by enzymes named desaturases.
Fatty acid oxidation (FAO): fatty acids are hydrolyzed step by step to generate acetyl-CoA, NADH, and $FADH_2$ used by the mitochondrial electron transport chain to produce energy.
Ferroptosis: iron-dependent type of programmed cell death triggered by lipid peroxidation that damages cellular membranes.
Follicular dendritic cells (FDCs): cells of stromal origin located in the central region of primary follicles and in the light zone of germinal centers; characterized by the ability to retain intact antigen for an extended period for presentation to germinal center B cells.
Glycolysis: glucose is hydrolyzed to pyruvate in aerobic conditions and lactate in anaerobic conditions to produce energy.
Immune checkpoints: ligands and receptors that regulate immune responses to avoid autoimmunity; actively participate in tumor immune evasion.

Table 1. (continued)

NF-κB-regulated metabolic genes				
Gene	Symbol	Biological context	Species	Refs
Prohibitin 2	*Phb2*	Regulation of cytochrome-c oxidase activity	mm	[19]
Serine hydroxymethyltransferase 2	*Shmt2*	Glycine synthesis	mm	[19]
Lactate dehydrogenase A	*Ldha*	Glucose metabolism	mm	[19]
Fatty acid synthase	*Fasn*	Fatty acid metabolism	mm	[19]
Solute carrier family 25 member 4	*Slc25a4*	ATP synthesis	mm	[19]
Pyruvate dehydrogenase kinase 1	*Pdk1*	Oxidative decarboxylation of pyruvate	mm	[19]
Metaxin 2	*Mtx2*	Mitochondrial transport	mm	[19]
Enolase 1	*Eno1*	Glucose metabolism	mm	[19]
Peroxiredoxin 6	*Prdx6*	Cell redox homeostasis	mm	[19]
Phosphoglucomutase 2	Pgm2	Carbohydrate metabolism	mm	[19]
Monoglyceride lipase	*Mgll*	Lipid metabolism	mm	[19]
Branched chain amino acid transaminase 1	*Bcat1*	Amino acid metabolism	mm	[19]
Proteasome 20S subunit beta 10	*Psmb10*	Proteasomal protein catabolism	mm	[19]
Aldehyde dehydrogenase 2 family member	ALDH2	Alcohol metabolism	HS/mm	[66]
Glutathione *S*-transferase theta 1	GSTT1	Glutathione metabolism	HS/mm	[66]
Glutathione *S*-transferase theta 3	GSTT3	Glutathione metabolism	HS/mm	[66]
Glutamic-oxaloacetic transaminase 1	GOT1	Amino acid metabolism	HS/mm	[66]
Solute carrier family 43 member 1	SLC43A1	Amino acid metabolism	HS/mm	[66]
Peptidyl arginine deiminase 4	PADI4	Cellular protein modification process	HS/mm	[66]
X-prolyl aminopeptidase 1	XPNPEP1	Bradykinin metabolism	HS/mm	[66]
Williams-Beuren syndrome chromosomal region 17 protein	WBSCR17 (GALNT17)	Protein glycosylation	HS/mm	[66]
ST8 alpha-*N*-acetyl-neuraminide alpha-2,8-sialyltransferase 4	ST8SIA4	Cellular protein modification process	HS/mm	[66]
Carbohydrate sulfotransferase 1	CHST1	Galactose metabolism	HS/mm	[66]
Carbohydrate sulfotransferase 10	CHST10	Carbohydrate biosynthesis	HS/mm	[66]
Molybdenum cofactor sulfurase	MOCOS	Molybdenum biosynthesis	HS/mm	[66]
Arsenite methyltransferase	AS3MT	Arsenic metabolism	HS/mm	[66]
Phosphatidylcholine transfer protein	PCTP	Lipid transport	HS/mm	[66]
Oxysterol binding protein like 3	OSBPL3	Bile acid biosynthesis	HS/mm	[66]
Ceramide synthase 6	CERS6	Ceramide biosynthesis	HS/mm	[66]
Solute carrier family 27 member 4	SLC27A4	Fatty acid metabolism	HS/mm	[66]
ATPase phospholipid transporting 10A	ATP10A	Lipid transport	HS/mm	[66]
Carnitine palmitoyltransferase 2	CPT2	Fatty acid metabolism	HS/mm	[66]
CD36 molecule	CD36	Fatty acid biosynthesis	HS/mm	[66]
Succinate dehydrogenase complex subunit D	SDHD	TCA cycle	HS/mm	[66]
NADH:ubiquinone oxidoreductase subunit S6	NDUFS6	OXPHOS	HS/mm	[66]

Immunotherapy: group of therapies that activate the patient's immune responses to counteract pathologies (e.g., cancer).
Inflammasome: cytosolic multimeric complex of innate immune cells that activates inflammatory responses.
Isotype-switching: process by which an activated plasma cell changes its antibody production from one class (isotype) to another.
Metabolic fitness: condition where cell metabolism addresses the energetic and biosynthetic demands of the cell, considering the nutrient availability in the microenvironment.
Myeloid-derived suppressor cells (MDSCs): heterogeneous subset of immature myeloid cells able to suppress immune responses; associated with cancer, infection, and inflammatory diseases.
Neutral lipids: nonpolar, usually stored in lipid droplets within the cell.
Oxidative phosphorylation (OXPHOS): process by which the synthesis of ATP is coupled to an electron transport chain driven by oxidation of metabolites.
Oxygen consumption rate (OCR): measures cellular respiration rate and mitochondrial function.
Reverse Warburg effect: biochemical process where, for example, cancer-associated stroma cells are metabolically coupled with adjacent cancer cells to support their growth.
Single-cell RNA sequencing: high-throughput technology used to profile RNA transcripts in individual cells of a given population to investigate heterogeneity.
Single-nucleotide polymorphisms: genomic variant at a single base position in the DNA.
Somatic hypermutation (SHM): process in the germinal center by which B cells enhance the diversity of their B cell receptor (BCR) repertoire through the accumulation of point mutations in the variable regions of both the heavy and light chains.
Spatial 'omics': 'omics' technologies aimed at visualizing RNA/protein/metabolite expression profiles within a tissue sample.
T follicular helper (Tfh): subset of $CD4^+$ T cells able to migrate into B cell follicles in the secondary lymphoid organ and facilitate germinal center reactions where they deliver 'help' signals to qualified B cells through cell–cell interactions.

Table 1. (continued)

NF-κB-regulated metabolic genes				
Gene	Symbol	Biological context	Species	Refs
5-Phosphohydroxy-L-lysine phospho-lyase	PHYKPL	Amino acid metabolism	HS/mm	[66]
Solute carrier family 15 member 5	SLC15A5	Peptide transport	HS/mm	[66]
Solute carrier family 1 member 5	SLC1A5	Amino acid transport	HS/mm	[66]
O-Linked *N*-acetylglucosamine (GlcNAc) transferase	OGT	Protein *O*-glcNAcylation	HS/mm	[66]
Lactotransferrin	LTF	Peptide transport	HS/mm	[66]
Ceruloplasmin	CP	Iron ion transport	HS/mm	[66]
Adenylate cyclase 3[b]	ADCY3	ATP conversion	HS/mm	[66]
Adenosylhomocysteinase[b]	AHCY	*S*-Adenosylhomocysteine cycle	HS/mm	[66]
Choline dehydrogenase[b]	CHDH	Glycine betaine biosynthesis	HS/mm	[66]
Guanylate cyclase 1 soluble subunit alpha 2[b]	GUCY1A2	GTP conversion	HS/mm	[66]
Inosine triphosphatase[b]	ITPA	Purine metabolism	HS/mm	[66]
Methylenetetrahydrofolate reductase[b]	MTHFD2	Folic acid metabolism	HS/mm	[66]
Natriuretic peptide receptor 1[b]	NPR1	cGMP biosynthesis	HS/mm	[66]
DNA polymerase alpha 1, catalytic subunit[b]	POLA1	DNA replication	HS/mm	[66]
RNA polymerase I subunit A[b]	POLR1A	DNA replication	HS/mm	[66]
RNA polymerase III subunit A[b]	POLR3A	DNA replication	HS/mm	[66]
RNA polymerase III subunit K[b]	POLR3K	DNA replication	HS/mm	[66]
Spermidine synthase[b]	SRM	Polyamine metabolism	HS/mm	[66]
PPARG coactivator 1 alpha	PPARGC1A	Energy metabolism	HS	[22]
Glutamic-oxaloacetic transaminase 2	GOT2	Amino acid metabolism	HS	[23]
Nuclear respiratory factor 1/2	NRF1/2	Transcription factor	HS	[24]
Transcription factor A, mitochondrial	TFAM	Transcription factor	HS	[24]
ATP synthase F1 subunit alpha	ATP5A1	ATP synthesis	HS/mm	[25]
Catalase	CAT	Oxidative stress response	HS/mm	[25]
Glucose transporter type 1	GLUT-1	Glucose transporter	HS/mm	[32]
Synthesis of cytochrome C oxidase 2	SCO2	OXPHOS	HS/mm	[33]
Carboxylesterase 1	CES1	Lipid metabolism	HS/mm	[34]
CCAAT enhancer binding protein beta	C/EBP	Energy metabolism	HS/mm	[37]
Glucose transporter type 3	GLUT-3	Glucose transporter	HS/mm	[67]
Stearoyl-CoA desaturase 1	SCD1	Fatty acid metabolism	HS/mm	[68]
Hexokinase 2	HK2	Glucose metabolism	HS	[69]
Solute carrier family 40 (iron-regulated transporter), member 1	SLC40A1	Iron metabolism	HS/mm	[70]
Aconitase isoform 2	ACO2	TCA cycle	HS	[71]
Isocitrate dehydrogenase 1/3A	IDH1/3A	TCA cycle	HS	[71]

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Tingible body macrophages (TBMs): large phagocytic macrophage able to actively phagocytose apoptotic lymphoid cells within the germinal center and therefore containing apoptotic bodies called tingible bodies.

Toll-like receptors (TLRs): class of transmembrane proteins that initiate the innate immune response by recognizing pathogen-associated molecular patterns derived from various microbes.

Table 1. (continued)

NF-κB-regulated metabolic genes				
Gene	Symbol	Biological context	Species	Refs
Succinate-CoA ligase ADP-forming subunit beta	SUCLA2	TCA cycle	HS	[71]
Glutamine-fructose-6-phosphate transaminase 2	GFPT2	Glutamine metabolism	HS	[72]
Aspartate beta-hydroxylase	ASPH (HAAH)	Calcium homeostasis	HS	[72]
Lipase G, endothelial type	LIPG	Lipid metabolism	HS	[72]
Nicotinamide phosphoribosyltransferase	NAMPT	NAD biosynthesis	HS	[72]
Glutaminase	GLS	Glutamine metabolism	HS/mm	[73]
Hexokinase 3	HK3	Glucose metabolism	HS/mm	[74]
Solute carrier family 25 member 1	SLC25A1	Mitochondrial citrate transporter	HS	[75]
ATP citrate lyase	ACLY	Acetyl-CoA biosynthesis	HS	[75]
Cytochrome P450 family 1 subfamily A member 1	*Cyp1a1*	Cytochrome P450	mm	[76]
Cytochrome P450 family 2 subfamily B member 1/2	*Cyp2b1/2*	Cytochrome P450	rn	[77]
Cytochrome P450 family 2 subfamily D member 5	*Cyp2d5*	Cytochrome P450	rn	[77]
Cytochrome P450 family 3 subfamily A member 7	CYP3A7	Cytochrome P450	HS	[78]
Cytochrome P450 family 27 subfamily B member 1	CYP27B1	Cytochrome P450	HS	[79]
NF-κB-regulated metabolic enzymes				
Gene	Symbol	Biological context	Species	Refs
6-Phosphofructo-2-kinase/ fructose-2,6-biphosphatase 3	PFKFB3	Glucose metabolism	HS/mm	[31]
Glucose-6-phosphate dehydrogenase	G6PD	NAPDH production	HS/mm	[41]
Hexokinase 2	Hk2	Glucose metabolism	mm	[41]

[a]Abbreviations: HS, *Homo sapiens*; mm, *mus musculus*; rn, *rattus norvegicus.*
[b]Predicted target genes.

centroblasts [15–17]. Since Rel nuclear translocation controls Myc expression during B cell activation [18], these findings suggest that Rel and Myc might cooperate in regulating anabolic metabolism and cell division in normal, autoreactive, malignant B cells of GC derivation.

REL amplifications and **single-nucleotide polymorphisms** in B cells are associated with human B cell lymphomas and autoimmune diseases [19]. A recent study provided direct evidence for the causal connection of *Rel* gain-of-function in GC B cells with the etiopathogenesis of autoimmune disease; conditional B cell-specific Rel overexpression from bacterial artificial chromosome (BAC)-transgenic loci in Rel^{TG};*CD19*-$Cre^{I/+}$ mice induced spontaneous GC reactions, enhanced GC responses to immunization, and a marked dose-dependent expansion of GC B cells and **isotype-switched** PCs. This resulted in increased serum antibody titers, spontaneous production of autoantibodies (including those associated with systemic lupus erythematosus and rheumatoid arthritis) and renal immune-complex deposition in mice, compared with wild type controls [19]. Notably, GC B cell-specific Rel gain was sufficient to rescue GC maintenance and terminal B cell

Box 2. Germinal center (GC)

GC is a transiently formed specialized microstructure localized in the follicles of secondary lymphoid tissues during T cell-dependent immune response [16,83] (Figure 1). Within the GC, B cells undergo the random process of **somatic hypermutation (SHM)** of the genes encoding their B cell receptors (BCR) and affinity maturation to produce high-affinity antibodies producing B cell clones for specific humoral immunity [16,83]. In fact, only B cells with increased antigen affinity are instructed to differentiate into long-lived antibody-secreting plasma cells (PCs) and memory B cells (MBCs). The GC requires a tight regulation to avoid hyper-responsiveness and autoimmunity [84]. In B cell follicles, B cells are supported by a specialized network of stromal cells named follicular dendritic cells (FDCs). When activated by an antigen, naïve B cells migrate to interfollicular areas where they interact with T helper cells through CD40-CD40L signals, which promotes B cell expansion. While part of the antigen–activated B-clones move to specialized areas in the lymph nodes where they differentiate into short-lived plasmablasts (PBs) secreting low-affinity antibodies, GC precursor B cells migrate into the center of the follicle to form an early GC. GC is divided in two distinct regions by day 7 after immunization: light zone (LZ) and dark zone (DZ) [84]. Within GCs, iterative rounds of mutation and selection occur via a cycle migration between the DZ where B cells undergo clonal expansion and SHM, and the LZ where positive selection occurs [16,83,84]. During positive selection, B cells capture antigen that is displayed on FDCs. The complex BCR–antigen is then internalized and the antigen is subsequently processed and presented as peptide fragments loaded on major histocompatibility II (MHCII), which enables B cells to receive help from T follicular helper cells (Tfhs). Selected LZ B cells are now marked as 'licensed' because they induce Myc to regulate GC maintenance and proliferation [16]. Selected LZ B cells then exit the GC reaction as PCs or MBCs or re-enter the DZ for further rounds of proliferation and SHM. This dynamic migration between DZ and LZ is known as cyclic re-entry. Unselected GC B cells go to apoptosis and are cleared by the tingible body macrophage (TBM) [84].

differentiation in otherwise constitutive *Rel* knockout mice, because crossing $Rel^{-/-}$ with Rel^{TG};*CD19*-$Cre^{I/+}$ mice, reconstituted GC B cell populations, **T follicular helper (Tfh)** cells, and PCs, underscoring the cell-intrinsic role of Rel in GC B cell lineages [19]. In agreement with findings in mouse loss-of-function models [15], Rel gain in GC B cells most prominently affected genes that controlled cell growth, G1/S transition, S and G2/M cell cycle progression, and anabolic metabolism, as shown by RNA-sequencing analysis of GC B cells from immunized Rel^{TG};*CD19*-$Cre^{I/+}$ and control *CD19*-$Cre^{I/+}$ mice [19] (Figure 1). Gene set enrichment analysis of RNA sequencing data demonstrated that nucleotide and amino acid metabolism were among the most enriched pathways in *Rel*-transgenic compared with control B cells [19]. Genes implicated in glucose transport, the regulation of glucokinase, and pyruvate and tricarboxylic acid (TCA) cycle metabolism were also significantly upregulated in *Rel*-overexpressing GC B cells [19] (Figure 1). Of note, *Myc* was among the top 10% upregulated genes in *Rel*-overexpressing GC B cells, with significant enrichment of Myc signatures, suggesting that Rel gain might exert at least some of its metabolic and pro-proliferative functions in GC B cells via Myc [19]. This places Rel as an important regulator of energy metabolism and cellular biosynthetic pathways in mouse GC B cells.

Several questions, however, remain unanswered. First, it is unclear whether the reported functions of RelA and NF-κB1 in B cell activation, GC maintenance, and terminal B cell differentiation (Figure 1) also involve the regulation of cell metabolism [15,20]. Given the importance of metabolism in oncogenesis and the high frequency of gene alterations leading to constitutive NF-κB activation in different types of B cell lymphoma and multiple myeloma [21], dissecting the metabolic functions of each NF-κB subunit in GC physiology and lymphomagenesis may help to identify actionable vulnerabilities for therapeutic intervention. Second, since NF-κB regulates the differentiation and function of non-B cell populations in GCs, such as Tfh cells, **follicular dendritic cells (FDCs)**, and **tingible body macrophages (TBMs)**, it will be important to determine whether and if so, how, NF-κB impacts their metabolic adaptations. Ultimately, as B cell states within distinct GC niches depend upon the metabolic demands dictated by the specific microenvironment and B cell developmental stage, it will be crucial to characterize phenotypes, interactomes, and metabolic networks that take place in the GC reaction and determine how these are affected by NF-κB at the single-cell level, using **single-cell RNA sequencing** and other single-cell and **spatial 'omics'** platforms. This information could guide the design of improved therapeutic approaches for treating lymphomas and autoimmune diseases.

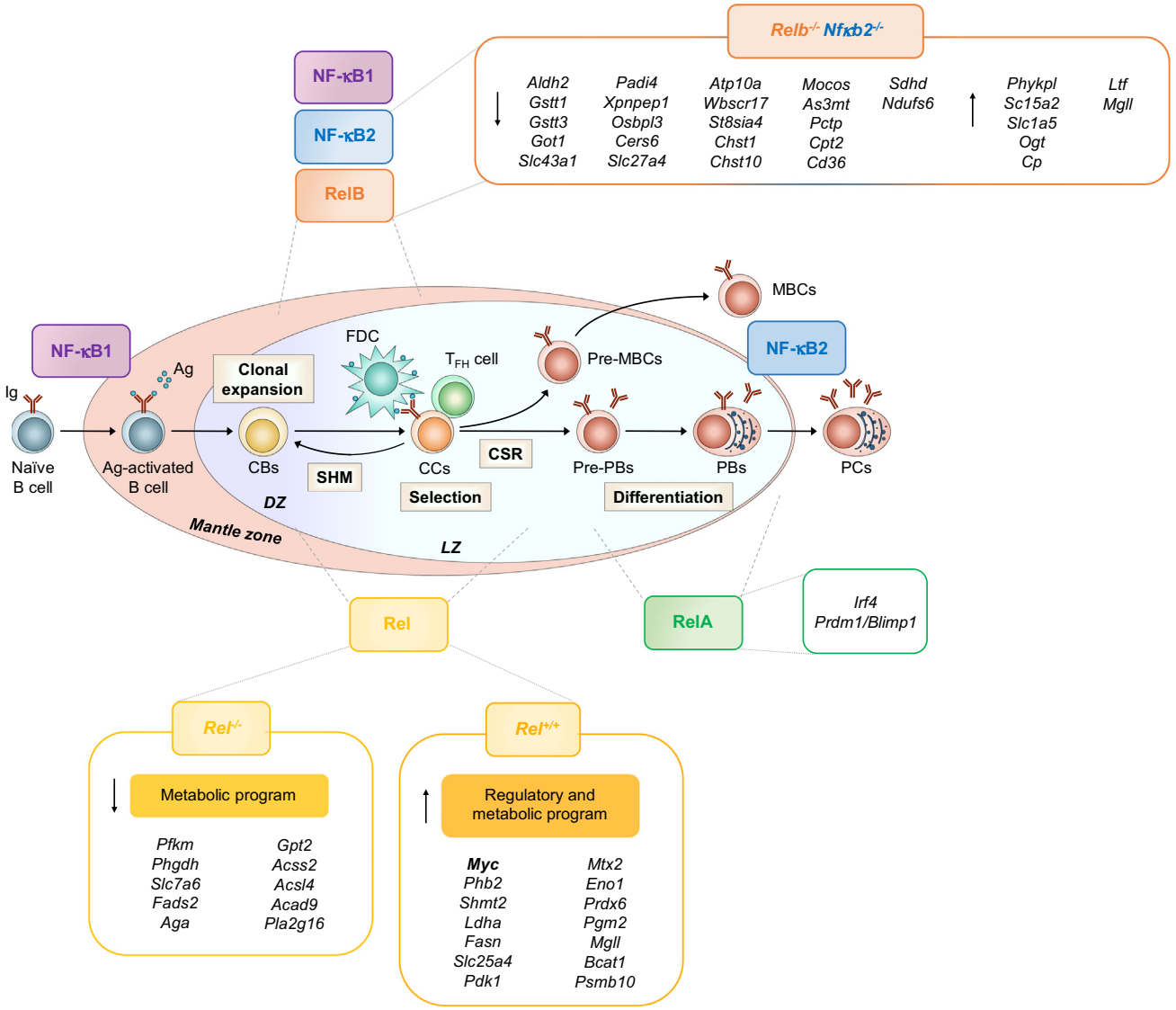

Figure 1. NF-κB transcription factors control the germinal center (GC) reaction. Schematic representation of GC initiation, maintenance, and differentiation (Box 2). GC is polarized into two distinct compartments. The dark zone (DZ) is the site of GC B cell proliferation and somatic hypermutation (SHM). Centroblasts (CBs) then enter the light zone (LZ) as centrocytes (CCs). In the LZ, CCs capture antigen displayed on follicular dendritic cells (FDCs), internalize, process, and subsequently present it to T follicular helper (Tfh) cells to undergo selection. Upon receiving survival signals from Tfh cells, CCs re-enter the DZ for further rounds of proliferation and SHM, after which they differentiate in either pre-plasmablasts (pre-PBs) and plasmablasts (PBs) or precursors of memory B cells (pre-MBCs) and ultimately exit the GC as memory B cells (MBCs) or high-affinity antibody-secreting plasma cells (PCs). All NF-κB subunits play essential roles in GC B cells, including GC maintenance (RelB, NF-κB1, and NF-κB2) and terminal B cell differentiation (RelA and NF-κB2). Specifically, Rel, RelB, and NF-κB2 are required for the maintenance of the GC reaction where they drive specific metabolic programs, while RelA controls the differentiation of GC B cells into PBs by regulating *Irf4* and *Pmdr1/Blimp1* [15,19,66,85]. Abbreviations: Ag, antigen; CSR, class-switch recombination; Ig, immunoglobulin.

Implications for hematological malignancies

Studies in cell lines have suggested that NF-κB drives lymphomagenesis in part by regulating cell metabolism. In a human acute T cell leukemia (ATL) cell line, *REL* knockout by CRISPR-Cas9 gene editing markedly impaired cell proliferation and mitochondrial metabolism, diminishing basal and maximal OCR, as well as ATP production [22]. Genome-wide microarray analysis

showed that among the genes most downregulated by *REL* knockout were those involved in OXPHOS, mammalian target of rapamycin complex 1 (mTORC1) signaling, and MYC activity. MYC target genes affected by *REL* knockout included the glucose transporter *GLUT1* and the master regulators of mitochondrial biogenesis, *PPARGC1A* and *TFAM* [22]. REL-containing NF-κB complexes were found to bind to the *MYC* promoter and upregulate *MYC* transcription as well as MYC protein amounts [22], while ectopic MYC expression rescued mitochondrial OCR and cell proliferation in *REL* knockout cells [22]; this suggested that REL might exert its metabolic functions in ATL cells at least in part via MYC.

Another study recently reported the MYC-independent metabolic reprogramming of diffuse large B cell lymphoma (DLBCL) and Hodgkin's lymphoma (HL) cells that was controlled by NF-κB [23]. NF-κB activation cooperated with signal transducer and activator of transcription (STAT)3 signaling in human lymphoma cells to increase glycolysis and glutaminolysis, in a program whereby glutamine drove anabolic processes and cell proliferation [23]. Indeed, in transformed MYC-deprived (MYC^{low}) P493-6 B cells (used to model MYC-independent lymphomas), co-ligation of IL-10 receptor (IL-10R) and **Toll-like receptor (TLR)**9, resulted in STAT3 and NF-κB activation, respectively. In turn, glutamine-derived carbons were incorporated into TCA cycle intermediates, including oxaloacetate, to generate amino acids and nucleobases, shown by metabolic and gene expression profiling [23]. This metabolic pathway was found to depend on NF-κB/STAT3-driven upregulation of the gene encoding aspartate transaminase 2, also known as *glutamic-oxaloacetic transaminase 2* (*GOT2*), which catalyzes glutamate and oxaloacetate conversion to α-ketoglutarate (αKG) and aspartate, the latter being a key precursor in nucleotide synthesis and, thereby, cell proliferation [23]. Pharmacological or genetic inhibition of either IKK/NF-κB or STAT3 decreased *GOT2* expression in IL-10+CpG-stimulated cells. Further, in chromatin immunoprecipitation experiments using IL-10R/TLR9-stimulated MYC^{low} P493-6 cells, phosphorylated STAT3 and RELA-containing NF-κB complexes bound to the proximal *GOT2* promoter to activate gene transcription, increasing cellular GOT activity [23]. Collectively, these findings imply that the NF-κB/STAT3 axis is essential for MYC-independent metabolic reprogramming, which drives proliferation of human lymphoma cells. They also identify GOT2 as a potential therapeutic target. Of note, unlike MYC-driven glutaminolysis, whereby glutamine is largely utilized to support energy production and **anaplerosis**, NF-κB/STAT3-driven glutaminolysis primarily supported anabolic functions, since aspartate and the nucleobases supplementation restored proliferation of glutamine deprived-MYC^{low}-P493-6 B cells. Conversely, OXPHOS was mainly fueled by fatty acids and other energy substrates, as shown by OCR analysis following FAO inhibition [23]. Metabolite rescue experiments under conditions of glutamine depletion or transaminase inhibition by *GOT2* knockdown or pharmacologic means indicated that this GOT2-dependent metabolic mechanism promoted proliferation of DLBCL and HL cell lines exhibiting constitutive NF-κB and STAT3 activation, due to environmental stimuli or oncogenic gene alterations. Accordingly, elevated *GOT2* expression was found in a subset of primary human DLBCL, HL, and Burkitt lymphoma samples and correlated with shorter survival in DLBCL patients, suggesting that GOT2 might be clinically relevant in lymphomagenesis.

In classical HL (cHL) constitutive NF-κB signaling was suggested to promote OXPHOS for ATP production and cell proliferation [24]. Nuclear genes encoding mitochondrial proteins, such as ATP synthase subunits and various components of other mitochondrial electron transport chain complexes, were found to be upregulated in cHL cell lines and primary human cHL cells compared with normal B cells. Interestingly, these cHL showed a corresponding increase in mitochondrial mass and in markers of mitochondrial biogenesis, including peroxisome proliferator activated receptor gamma coactivator-1 (PGC-1)α/β, nuclear respiratory factors (NRF)-1/2, and mitochondrial transcription factor A (TFAM). Accordingly, cHL cell lines displayed higher OCR and lower lactate production than non-HL cell lines and relied upon oxidative metabolism for ATP production, cell

survival, and proliferation [24]. Treatment of cHL cell lines with NF-κB inhibitors, such as SN50 and IKK-NBD, at nontoxic concentrations reduced the expression of mitochondrial proteins, diminished OCR and mitochondrial biogenesis, and increased lactate production [24]. Collectively, these results suggest that NF-κB is important in the metabolic reprogramming of Hodgkin-Reed-Sternberg cells (tumor cells of cHL) [24]. A similar metabolic profile characterized by limited glycolytic activity and a reliance on mitochondrial metabolism for cell survival and proliferation was recently reported in primary chronic lymphocytic leukemia (CLL) cells, CLL cell lines, and tumor cells from patients with Richter syndrome (RS) [25], a complication whereby CLL transforms into an aggressive type of DLBCL with poor clinical outcomes, limited treatment options, and frequent NF-κB-activating gene mutations [26]. Due to the central role of aberrant NF-κB activation in CLL etiopathogenesis and RS transformation, with RELA being the dominant NF-κB subunit in these clinical contexts, NF-κB represents an attractive therapeutic target in CLL. Treatment with the selective REL/RELA inhibitor, IT-901, which exhibits antilymphoma activity in preclinical models [27,28], was shown to trigger a dose-dependent induction of apoptosis in primary human CLL and RS cells and CLL cell line models, with no apparent toxicity to normal B and T lymphocytes and stromal cells [25]. These *in vitro* results were recapitulated by *RELA* knockdown in CLL cell lines and systemic IT-901 treatment in xenograft and patient-derived xenograft models of CLL and RS, respectively, *in vivo* [25]. In both CLL lines and primary cells, the cytotoxic effects of IT-901 were accompanied by an increase in mitochondrial reactive oxygen species (ROS) formation and a corresponding decrease in mitochondrial membrane potential, maximal OCR, and ATP production [25]. The IT-901-dependent reduction of OXPHOS in CLL cells was also associated with the downregulation of NF-κB-regulated genes, including those encoding cytochrome c oxidase assembly subunit 2 (SCO2), the ATP-synthase, ATP5A1, and the ROS scavenger, catalase (CAT) [25].

While these studies underscore the potential clinical utility of targeting NF-κB-driven metabolic programs in cancer patients, translating this knowledge into healthcare benefit in lymphoma patients will require further investigations using primary tumor samples and clinically relevant experimental models, such as patient-derived 3D organoid cocultures. It will also require the development of rational biomarker strategies for patient stratification and the utilization of single-cell and spatially resolved analytical technologies to relate the effects of new drugs to the states of malignant and nonmalignant cells in the tumor microenvironment (TME). The metabolic characterization of DLBCL subsets is a first step in this direction [29,30] for ultimately developing precision medicine that selectively targets NF-κB signaling in cancer to improve the management of oncological patients.

NF-κB and metabolic adaptations in cancer

Recent studies have shown that NF-κB plays a central role in the response of tumor cells to nutrient-depleted microenvironments by orchestrating metabolic programs that impact glycolysis, glutaminolysis, OXPHOS, and other metabolic pathways.

IKKβ is activated by glutamine deprivation to promote cell survival during low-glutamine availability via a mechanism that is independent of NF-κB [31]. Indeed, in glutamine-starved human fibrosarcoma HT1080 cells, IKKβ bound to and phosphorylated 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase isoform 3 (PFKFB3), a key driver of glycolysis, at Ser269, inhibiting PFKFB3 activity (Figure 2A) [31]. In the same cell line, this IKKβ-dependent adaptation diminished glycolysis and lactate production when glutamine concentrations were low, redirecting glucose-derived carbons to the TCA cycle and the pentose phosphate pathway, thereby reducing glutamine dependence for the generation of TCA cycle intermediates and the suppression of ROS [31]. Consistently, co-inhibition of IKKβ and glutamine metabolism resulted in the synergistic killing of cancer cells, *in vitro* and *in vivo* [31]. This established an important role for IKKβ in sensing glutamine

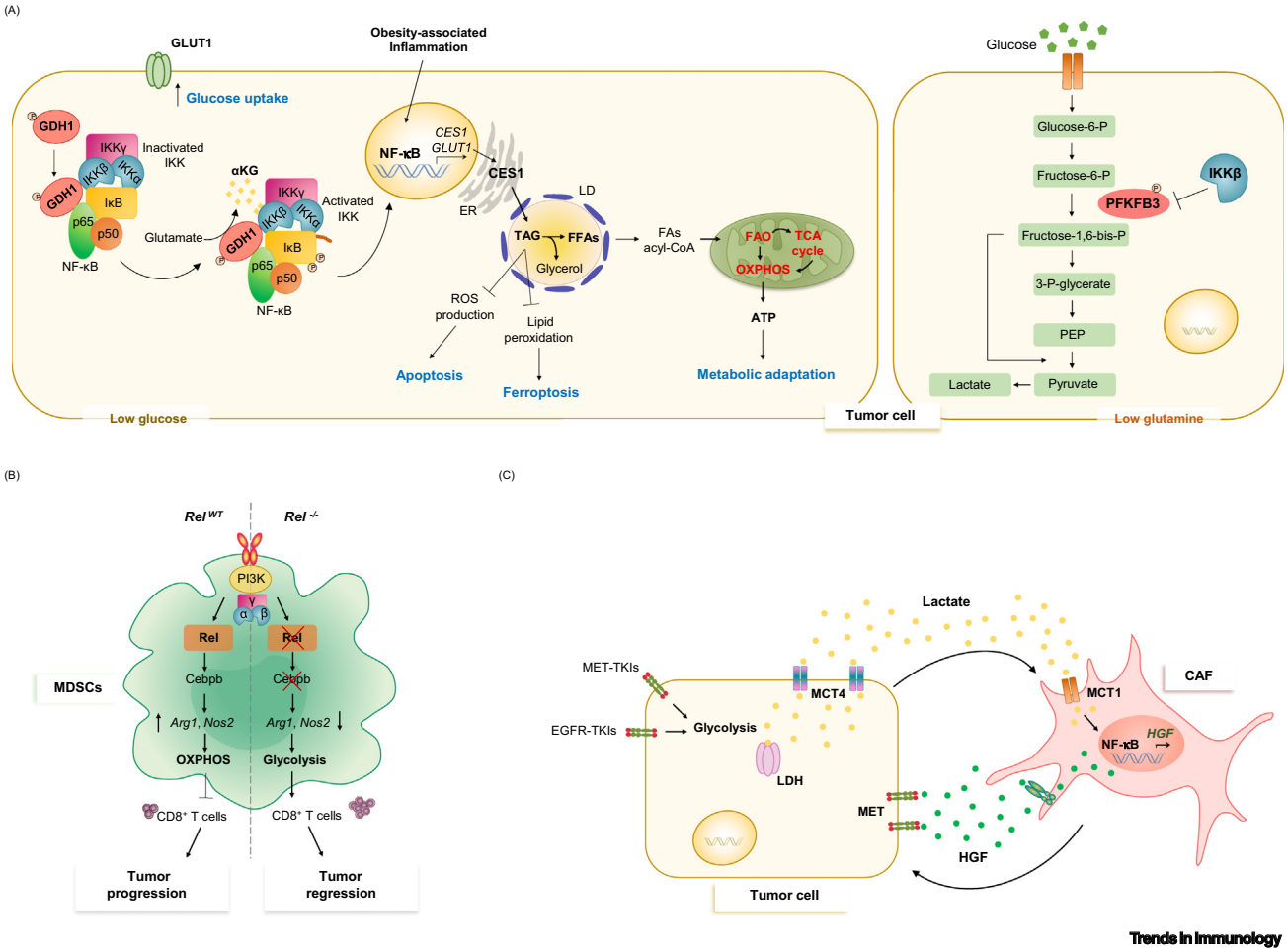

Figure 2. NF-κB coordinates metabolic responses within the tumor microenvironment (TME). (A) IκBα kinase (IKKβ)/NF-κB is activated in response to nutrient deprivation (low glucose or low glutamine) by inflammatory and metabolic stimuli [(i.e., α-ketoglutarate (αKG)] [32]. In turn, IKKβ/NF-κB promotes metabolic adaptation by either upregulating metabolic target genes (i.e., *CES1* and *GLUT1*) or regulating the activity of metabolic enzymes (i.e., PFKFB3) [32,34]. (B,C) NF-κB transcription factors also operate in the noncancerous cells within the TME. Rel regulates MDSC metabolism and suppressive functions via Cebpb, which in turn activates *Arg1* and *Nos2* [37] (B). Activation of RelA in cancer-associated fibroblasts (CAFs) by tumor cell-released lactate is responsible for increased HGF production. HGF, in turn, activates MET-dependent signaling in tumor cells and this metabolic crosstalk between CAF and tumor cell can promote drug resistance [44] (C). Abbreviations: αKG: α-ketoglutarate; Arg1, arginase 1; Cebpb, CCAAT enhancer binding protein beta; CES1, carboxylesterase 1; EGFR, epidermal growth factor receptor; ER, endoplasmic reticulum; FAs, long-chain fatty acids; FAO, fatty acid oxidation; FFAs, free fatty acids; GDH1, glutamate dehydrogenase 1; GLUT1, glucose transporter 1; HGF, hepatocyte growth factor; LD, lipid droplet; LDH, lactate dehydrogenase; MCT1, monocarboxylate transporter 1; MCT4, monocarboxylate transporter 4; MDSCs, myeloid-derived suppressor cells; MET, mesenchymal–epithelial transition; Nos2, nitric oxide synthase 2; OXPHOS, oxidative phosphorylation; PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3; ROS, reactive oxygen species; TAG, triacylglycerol; TCA, tricarboxylic acid cycle; TKIs, tyrosine kinase inhibitors.

limitation-induced metabolic stress and promoting adaptive response mechanisms to enable tumor cell survival. Similarly, under low-glucose conditions, glutamate dehydrogenase 1 (GDH1), a key enzyme in glutaminolysis that converts glutamate to αKG, is phosphorylated at Ser384 and physically interacts with both RELA and IKKβ [32]. Upon these interactions, GDH1-produced αKG binds to and activates IKKβ, thereby inducing NF-κB signaling, which in turn promotes glucose uptake and glioblastoma cell survival by upregulating glucose transporter 1 (GLUT1) (Figure 2A) [32]. This IKKβ/NF-κB-dependent mechanism has been deemed important in gliomagenesis, since IKKβ-depleted human U87/EGFRvIII (constitutively active truncated EGFR mutant) glioblastoma cells reconstituted with an IKKβ mutant incapable of binding to αKG exhibited reduced glucose uptake, glioblastoma cell survival, and slower tumor growth *in vivo*

upon intracranial injection in nude mice [32]. Accordingly, GDH1 Ser384 phosphorylation was linked to a more aggressive glioblastoma in patients [32]. These findings revealed a mechanism of metabolite-induced NF-κB activation and a metabolic role for NF-κB signaling in brain cancer progression [32].

Early observations in tumor cell lines suggested that NF-κB contributes to colorectal carcinoma (CRC) pathogenesis in part by promoting metabolic adaptation to energy stress [33]. Recently, we showed that this NF-κB-dependent adaptative mechanism is hardwired to the regulation of lipid metabolism, as evidenced from the altered lipidomic profiles of RelA/RELA-deficient mouse embryonic fibroblasts and human CRC cell lines [34]. Also, evidence of an ancient connection between nutrient imbalance and lipid metabolism mediated via NF-κB was recently provided in *Drosophila melanogaster*, where NF-κB/Relish was shown to play a central role in the metabolic adaptation to fasting by restraining triacylglycerol lipolysis via repression of the gene encoding adipose triglyceride lipase (ATGL)/Brummer in the fat body [35]. This metabolic mechanism is known to preserve cellular triacylglycerol reservoirs, the major source of energy in metazoans [35]. Contrary to the outcome of this ancient adaptive response in insects, NF-κB activation in human CRC cell lines can increase triacylglycerol lipolysis during nutrient deprivation, thereby mobilizing endogenous free fatty acids (FFAs) from lipid droplets and fueling FAO and OXPHOS for energy provision [34]. Accordingly, NF-κB inhibition impaired lipolysis during energy stress, diminishing OXPHOS flux and mitochondrial ATP production and ultimately resulting in metabolic crisis and cell death [34]. By combining a metabolomic and a transcriptomic screen, we identified carboxylesterase 1d (Ces1d), the murine ortholog of human CES1, as an NF-κB-regulated lipase promoting cancer cell survival and adaptation to nutrient limitation in aggressive human CRC [34]. We found that elevated *CES1* expression, as well as NF-κB activity, were enriched in metastasis-prone CRC consensus molecular subtype (CMS)4, associated with obesity, epithelial-to-mesenchymal transition (EMT), inflammation, and worse clinical outcomes in CRC patients [34]. Elevated *CES1* expression also correlated with shorter overall survival in overweight, but not non-overweight CRC patients, suggesting a role for NF-κB/CES1-dependent fat catabolism in the clinical evolution of CRC in obese patients. Mechanistically, Ces1d/CES1 mediated CRC cell survival by: (i) increasing triacylglycerol and cholesterol ester lipolysis to mobilize endogenous FFAs and fuel FAO to meet the energy demand during starvation; and (ii) preventing the toxic accumulation of **neutral lipids** that leads to ROS production and phospholipid peroxidation, triggering apoptosis and **ferroptosis**, respectively (Figure 2A). Accordingly, genetic, or pharmacologic Ces1d/CES1 inhibition induced CRC cell death upon starvation *in vitro* and CRC growth suppression in mouse models *in vivo*, suggesting that CES1 might be a candidate target for treating CRC.

Collectively, these studies underscore the central role of the IKKβ/NF-κB pathway as a sensor of metabolic imbalance and a chief coordinator of adaptive responses aimed at restoring cancer cell survival in the face of continual environmental changes (Figure 2A). Future studies may help determine whether these IKKβ/NF-κB-dependent metabolic driving malignancy, metastasis, and therapy resistance, might be translated into more effective anticancer treatments.

NF-κB in cancer immunometabolism

Immunotherapy has revolutionized the management of cancer patients. **Adoptive cell transfer** and **immune checkpoint** inhibitors have resulted in durable clinical responses and even cures for certain cancers. However, the efficacy of these therapies varies substantially among cancer patients, with only a minority of them receiving clinical benefit [36]. The metabolic reprogramming of immune cells that occurs during activation and differentiation profoundly affects immune functionalities and, consequently, the clinical outcome of cancer patients [36]. Thus, manipulating

metabolic pathways involved in TME-dependent immunosuppression represents an attractive strategy to enhance the clinical efficacy of current immunotherapies.

A recent study demonstrated that Rel is a myeloid-based immune checkpoint [37] (Figure 2B). It was shown that myeloid cell-specific *Rel* depletion reduced tumor growth in B16F10 cell melanoma-bearing LysM-Cre/$Rel^{F/F}$ mice [37]. This antitumor effect of *Rel* loss depended on the Rel-mediated control of the generation, function, and metabolism of **myeloid-derived suppressor cells (MDSCs)**, which promote tumorigenesis by suppressing antitumor cytotoxic immune responses [37]. Both $Rel^{-/-}$ and LysM-Cre/$Rel^{F/F}$ mice displaying global and myeloid-specific *Rel* deletion, respectively, exhibited significantly reduced numbers of MDSC cells and correspondingly increased percentages of activated $CD8^+$ effector T cells in the TME. Notably, $Rel^{-/-}$ MDSCs profoundly reprogrammed their metabolism, diminishing OXPHOS flux and mitochondrial ATP production, while increasing glycolysis, relative to wild type cells [37]. Among the genes that were most downregulated in $Rel^{-/-}$ MDSCs compared with control cells were those encoding factors involved in glucose, amino acid, and lipid metabolism, while upregulated genes included cell cycle checkpoint and proinflammatory genes [37]. Mechanistically, Rel promoted the formation of an enhanceosome complex that also included RelA/p65, NF-κB1/p50, Stat3, and CCAAT enhancer binding protein beta (*Cebpb*), a master transcription factor for MDSC differentiation, to drive the expression of MDSC signature genes such as *Cebpb* and *Arginase 1* [37]. Accordingly, *Cebpb* expression was markedly reduced in *Rel*-deficient MDSCs, while C/EBPβ overexpression in *Rel* knockout MDSCs isolated from LysM-Cre/$Rel^{F/F}$ mice effectively rescued their phenotype, reducing glycolysis and increasing OXPHOS and expression of proinflammatory cytokines [37]. Importantly, C/EBPβ overexpression also restored the immunosuppressive activity of *Rel*-deficient MDSCs against T cells, as shown by the decreased proliferation of activated $CD8^+$ T cells cocultured with *Cebpb*-overexpressing $Rel^{-/-}$ ($Rel^{-/-}$+Cebpb) MDSCs compared with $Rel^{-/-}$ MDSCs [37]. These findings support the idea that OXPHOS-based metabolism is a key feature of immunosuppressive cells, as also reported for T regulatory cells and anti-inflammatory (M2-like) tumor-associated macrophages (TAMs) [38]. Of note, a previous study reported a similar myeloid-specific, NF-κB-dependent immune checkpoint that restricts $CD8^+$ T cell trafficking into tumors [39,40]. Myeloid-specific depletion of the NF-κB-target gene *Gadd45b* was shown to increase TAM proinflammatory activation and intratumoral T cell infiltration while diminishing tumorigenesis in several mouse cancer models [39,40]. However, while this study identified alterations in the expression of immunomodulatory metabolic genes, such as *Arginase 1*, *Nitric Oxide Synthase 2*, *Heme oxygenase-1*, *Indoleamine 2,3-dioxygenase*, and *Cyclooxygenase 2*, it did not investigate changes in respiratory and glycolytic metabolism of TAMs [39,40].

Metabolic reprogramming toward glycolysis is a pivotal mechanism shaping T-cell immune responses. A recent study demonstrated that in *Map3k14//Atg5*^{tKO} (*Map3k14*$^{F/F}$;*Atg5*$^{F/F}$ *CD4*$^+$-Cre) mice, harboring T-cell-specific deletion of the NF-κB-inducing kinase (NIK)-coding gene and bearing B16F10 melanoma, NIK deficiency impaired the reprogramming of TME-based $CD8^+$ effector T cells toward glycolysis, as shown by the measurement of basal and maximum ECAR in $CD8^+$ T cells isolated from tumors. Accordingly, these cells were hypofunctional when challenged by *Listeria monocytogenes* infection [41]. Reciprocally, ectopic NIK expression in *Map3k14*^{tg};*ER*-Cre (*R26Stop*^{FL};*Map3k14*^{tg};*ER*-Cre) mice restored $CD8^+$ T-cell metabolism by increasing both ECAR and OCR and repristinated T cell effector function, since NIK-induced transgenic (NIK^{iTg}) $CD8^+$ were found to be fully competent in IFN-γ production, thereby restoring antitumor immunity and the efficacy of adoptive T cell therapy [41]. Indeed, ectopic NIK expression diminished tumor growth and improved animal survival in MC38 CRC and B16F10 melanoma syngeneic models, while increasing the frequency of tumor-infiltrating $CD4^+$ and $CD8^+$ T cells and IFN-γ-producing $CD8^+$ T cells. Additionally, adoptive transfer of NIK^{iTg} $CD8^+$ T cells expressing

the Pmel1 transgenic T cell receptor that recognizes the gp100 melanoma antigen reduced tumor growth and increased the number of tumor-infiltrating and IFN-γ-producing $CD8^+$ effector T cells in melanoma-bearing mice compared with the adoptive transfer of wild type $CD8^+$ Pmel1 transgenic T cells [41]. NIK-dependent regulation of T cell **metabolic fitness** did not involve NF-κB, but rather, involved the control of intracellular ROS concentrations via the glucose-6-phosphate dehydrogenase (G6PD)/NADPH antioxidant system and the inhibition of hexokinase 2 (Hk2/HK2) autophagic degradation. [41]. Consistently, in mice carrying an *Nfkb2* point mutation that prevents NIK-induced NF-κB2/p100 proteolytic processing ($Nfkb2^{Lym1/+}$), *Hk2* and *G6pd* expression were normal [41].

NF-κB in metabolic crosstalk within the TME

Cancer and stromal cells within tumors interact metabolically via a bi-directional transfer of metabolites. This key role of the TME in shaping cancer cell metabolism and vice versa is an established hallmark of cancer [42]. Cancer-associated fibroblasts (CAFs) were the first type of stromal cells reported to be metabolically coupled with cancer cells as part of the so-called '**reverse Warburg effect**' [43]. Recently, it was shown that, upon extended treatment with tyrosine kinase inhibitors (TKIs), such as the MET inhibitor JNJ-605, epidermal growth factor receptor (EGFR)- or MET receptor-tyrosine kinase-addicted human non-small cell lung carcinoma (NSCLC) cells RES-J EBC1 shifted their metabolism toward glycolysis, increasing lactate production [44]. In this context, secreted lactate was shown to be a key metabolite instructing CAFs to produce hepatocyte growth factor (HGF) in an NF-κB-dependent manner [44]. In turn, increased HGF, which activates MET-dependent signaling in cancer cells, perpetuated resistance to TKIs [44] (Figure 2C). Accordingly, genetic or pharmacological inhibition of molecules involved in this lactate-dependent axis, such as lactate dehydrogenase (LDH), monocarboxylate transporter 4 (MCT4), and monocarboxylate transporter 1 (MCT1), abrogated JNJ-605 resistance in NOD-SCID mice bearing RES-J EBC1 [44]. Of note, HGF and MCT4 were overexpressed in stromal and tumor cells, respectively, from patients with advanced NSCLC who progressed on EGFR TKI treatment, demonstrating the clinical relevance of these findings [44].

Collectively, these studies underscore how the regulation of cell metabolism is a key mechanism by which NF-κB drives tumorigenesis and therapy resistance. Indeed, while on the one hand, NF-κB-dependent metabolic programs sustain proliferation, stemness, survival, and metabolic adaptation of cancer cells during energy stress, on the other hand, it promotes immunosuppression and therapy resistance by operating in nonmalignant cell types of the TME [31,32,34,37,41,44]. Since therapeutically targeting the NF-κB pathway has been shown to produce preclusive on-target toxicities, an improved understanding of the cancer-specific activators and effectors of NF-κB-mediated metabolic signaling should be an effective strategy to identify actionable targets for candidate therapeutic intervention in cancer patients.

NF-κB and inflammasome metabolic regulation

Immune cells reconfigure their metabolism in response to inflammatory stimuli to generate ATP, maintain redox balance, and create biomass for sustaining proliferation and launching immune effector functions. **Inflammasomes** play essential functions in regulating immune responses and maintaining homeostasis. A large body of evidence indicates that inflammasomes, the best characterized being the NOD-, LRR-, and pyrin domain-containing protein (NLRP)3 inflammasome, also respond to a wide variety of metabolic stimuli (Figure 3) [45–48]. As NF-κB signaling plays a crucial role in the priming phase of inflammasome activation, during which TLR-induced NF-κB activation is responsible for transcriptional upregulation of the genes encoding NLRP3 and pro-IL-1β, the NF-κB system represents a pivotal node linking metabolic cues with

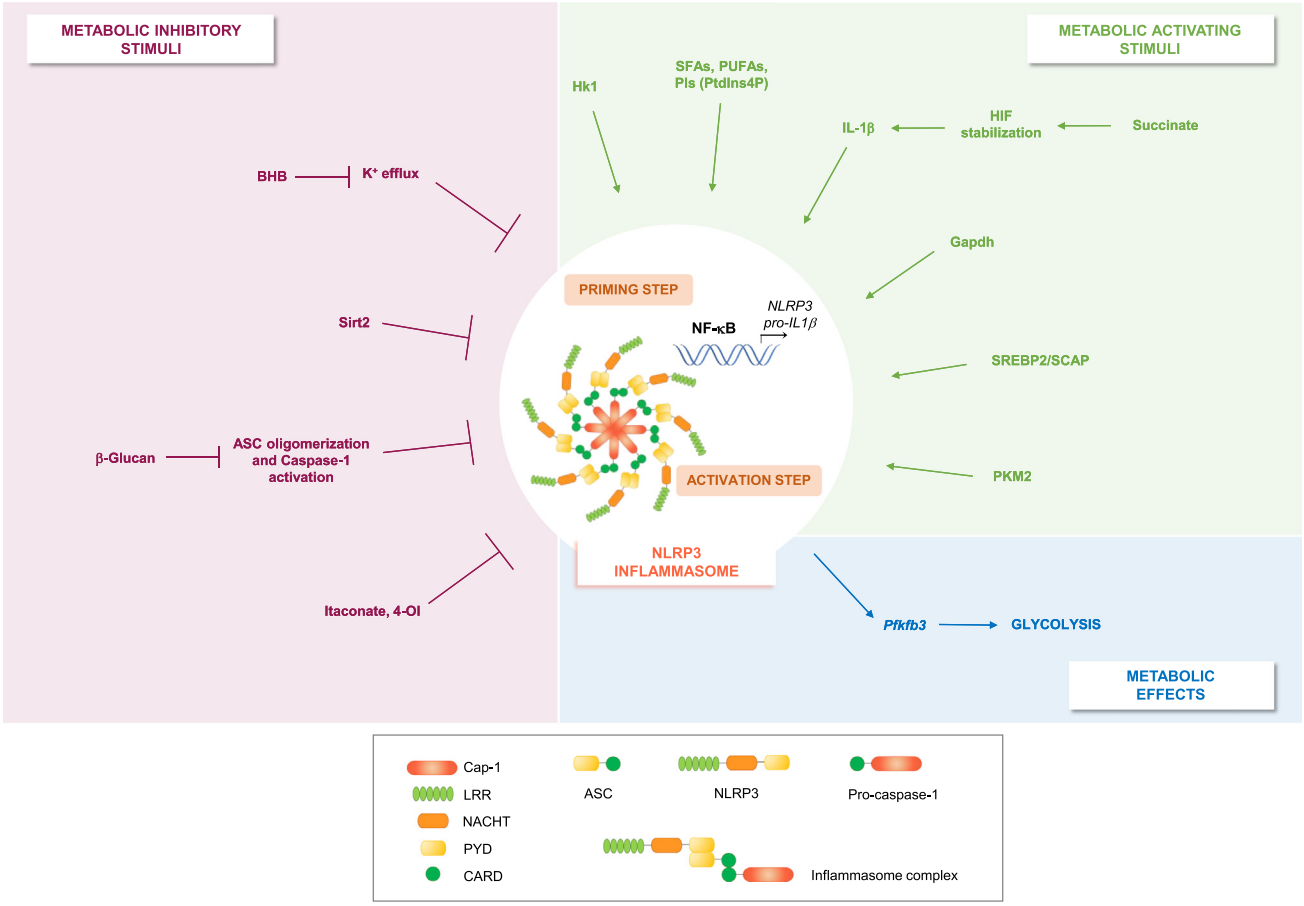

Figure 3. Metabolic stimuli regulate NF-κB/NACHT, LRR, and PYD domains-containing protein (NLRP3) inflammasome activity. Upon exposure to activating stimuli, innate immune cells activate NLRP3 inflammasomes in a two-step process consisting of a priming and an activation phase. The NF-κB pathway plays a crucial role in the priming phase by upregulating genes encoding NLRP3 and pro-IL-1β. During the subsequent activation phase, pro-caspase 1 (pro-Cap-1) is recruited by apoptosis-associated speck-like protein containing (ASC) via a CARD-CARD interaction, allowing the assembly of the functional inflammasome complex, comprising NLRP3, ASC, and pro-Cap-1 [86]. Ultimately, inflammasome activation leads to caspase 1-dependent secretion of proinflammatory cytokines, IL-1β and IL-18, and the induction of a gasdermin D-mediated form of cell death known as pyroptosis. Several metabolic stimuli can activate (green) or inhibit (violet) NLRP3 inflammasome [50,51,53–61]. In turn, once activated, inflammasome controls metabolism (blue) of innate immune cells. Abbreviations: BHB, β-hydroxybutyrate; CARD, caspase activation and recruitment domain; Gapdh, glyceraldehyde-3-phosphate dehydrogenase; HIF, hypoxia-inducible factor; Hk1, hexokinase 1; IL-1β, interleukin-1β; K, potassium; LRR, C-terminal leucine-rich repeat; NACHT, neuronal apoptosis inhibitor protein (NAIP), MHC class 2 transcription activator (C2TA), incompatibility locus protein from *Podospora anserine* (HET-E), and telomerase-associated protein (TP1); 4-OI, 4-octyl itaconate; *Pfkfb3,* 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3; PIs, phosphatidylinositol; PKM2, pyruvate kinase M2; PtdIns4P, phosphatidylinositol-4-phosphate; PUFAs, polyunsaturated fatty acids; PYD, amino-terminal pyrin domain; SCAP, REBP cleavage-activating protein; SFAs, saturated fatty acids; Sirt2, Sirtuin 2; SREBP2, sterol regulatory element-binding protein 2.

inflammasome-driven cellular responses in physiology and disease. While transient, balanced inflammasome activation serves an important homeostatic purpose and persistent, uncontrolled inflammasome activity is a hallmark of both genetic and more complex inflammasome-associated diseases [45]. As such, it is of paramount importance to understand how inflammasome activation is regulated and how it may be inhibited therapeutically [49].

Several glycolytic enzymes, including Hk1, pyruvate kinase M2 (PKM2), and glyceraldehyde-3-phosphate dehydrogenase (*Gapdh*), have been reported to regulate inflammasome activation

[48,50,51]. In turn, inflammasome activation can reprogram macrophage metabolism towards glycolysis through *Pfkfb3* [52]. Accordingly, both the NLRP3 inflammasome inhibitor, MCC950, and the PFKFB3 inhibitor, 3PO, attenuate lipopolysaccharide (LPS)- and amyloid-β (Aβ)-induced glycolysis as shown by the analysis of ECAR, OCR, and IL-1β secretion in bone marrow-derived macrophages (BMDMs) [52]. Reduced glycolysis and Il-1β secretion have also been observed in BMDMs isolated from *Nlrp3*- and *Il1r1*-deficient mice [57].

In addition to enzymes, metabolites can themselves stimulate inflammasome activation. For instance, β-glucan, a natural polysaccharide of the fungal cell wall of *Candida albicans* known to induce innate immune memory, has been shown to suppress NLRP3 activation by blocking ASC oligomerization and caspase-1 activation in primed macrophages *in vitro*, as well as in macrophages isolated from patients with **cryopyrin-associated periodic syndrome (CAPS)**. These findings suggest that β-glucan is a promising and affordable novel candidate for treating NLRP3-related disorders [53]. TCA cycle intermediates, including succinate and β-hydroxybutyrate (BHB), have also been implicated in the regulation of inflammasome activity [54,55]. Further evidence has shown that endogenous molecules such as the TCA derivative itaconate and its prodrug 4-octyl itaconate (4-OI), can inhibit NLRP3 inflammasome activation in LPS-primed BMDMs [56]. 4-OI was also shown to block NLRP3-dependent IL-1β release in peripheral blood mononuclear cells from CAPS patients and diminish inflammation in a mouse model of urate-induced peritonitis [56]. These findings suggest that targeting NLRP3 with itaconate might hold therapeutic potential for treating certain human diseases [56].

Cholesterol metabolism is yet another pathway that can orchestrate inflammasome activation. It was recently shown that the maturation of sterol regulatory element-binding protein 2 (SREBP2), the master transcription factor of cholesterol metabolism, is closely integrated with NLRP3 inflammasome activation, both *in vitro* and *in vivo* [57]. It was reported that NLRP3 forms a ternary complex with REBP cleavage-activating protein (SCAP) and SREBP2, which, in turn, translocates to the Golgi apparatus proximally to a mitochondrial cluster for efficient inflammasome assembly [57]. Therefore, besides controlling cholesterol biosynthesis, SCAP-SREBP2 operates in macrophages as a regulatory node that integrates cholesterol metabolism with inflammation [57]. Accordingly, cholesterol depletion or treatment with statins, which enforces cholesterol biosynthetic signaling, promotes NLPR3 inflammasome activation. Conversely, synthetic SCAP-SREBP2 inhibitors and endogenous sterols, including cholesterol and 25-HC, suppress this process *in vitro* and *in vivo* [57].

Another class of metabolites involved in the modulation of inflammasome activity includes saturated fatty acids (SFAs), polyunsaturated fatty acids (PUFAs), and phosphatidylinositols [47,58,59]. Excess of SFA-derived intracellular crystals stimulated NLRP3 activation and IL-1β release in primary murine macrophages *in vitro*, as well as IL-1β secretion and acute inflammation *in vivo*. In contrast, treatment with oleic acid reversed this phenotype [59]. Using a combination of complementary experimental approaches, multiple stimuli caused the disassembly of the *trans*-Golgi network (TGN), where negatively charged phosphatidylinositol-4-phosphate (PtdIns4P) bound the polybasic region of NLRP3, subsequently recruited to the dispersed TGN (dTGN) [60]. Accordingly, upon disruption of the interaction between NLRP3 and PtdIns4P, both NLRP3 assembly and downstream inflammasome signaling were inhibited [60]. Thus, recruitment of NLRP3 to the dTGN is an early and common event in NLRP3 activation.

In addition, the NLRP3 inflammasome can be regulated by nutrient sensors, such as Sirtuin 2 (Sirt2) [50,61]. Using a newly developed coculture system that modeled the effects of

inflammation on insulin resistance in adipose tissue during aging and aging mouse models, a recent study demonstrated that NLRP3 acetylation was involved in aging-associated inflammation and insulin resistance in macrophages [61]. Moreover, NLRP3 deacetylation by Sirt2, a NAD^+-dependent deacetylase, prevented inflammation and insulin resistance in aged mice, but not in young mice. These findings suggested that dysregulation of NLRP3 acetylation might contribute to aging-associated metabolic inflammation and underscored the potential of targeting the SIRT2-NLRP3 axis in macrophages, as a putative effective strategy to reverse age-associated inflammation [61].

Although it is well recognized that metabolism plays a major role in regulating the NLRP3 inflammasome, and several stimuli have been characterized as either positive or negative regulators of inflammasome activity, there is still limited knowledge about how activation of the NLRP3 inflammasome can modulate cell metabolism. Filling in these gaps will be important for devising effective strategies to target the inflammasome system in human disease.

Concluding remarks

A wealth of studies in recent years has highlighted how the IKK/NF-κB system is hardwired to control local and systemic metabolic networks that shape organismal physiology, cell differentiation, energy homeostasis, and an array of human pathologies ranging from type 2 diabetes and obesity, to chronic inflammatory diseases, autoimmunity, and cancer. In this framework, NF-κB signaling appears to be particularly important in governing metabolic adaptations to environmental changes and disruptions of tissue homeostasis that occur in disease. Given the pervasive role of aberrant NF-κB activity in malignant and nonmalignant pathologies [11,62,63], an increased understanding of how NF-κB regulates metabolism may inform the development of therapeutic targets and diagnostic tools for various conditions. Despite an aggressive effort by the pharmaceutical industry over the last three decades to develop specific IKK/NF-κB inhibitors, none have been clinically approved, due to the preclusive, on-target toxicities of drugs blocking core components of the IKK/NF-κB pathway. As such, the in-depth characterization of IKK/NF-κB-dependent metabolic drivers of disease would seem a logical first step toward identifying actionable candidate targets in the NF-κB pathway, ideally circumventing the preclusive toxicities of conventional IKK/NF-κB-targeting drugs.

However, several important questions remain unanswered (see Outstanding questions). For instance, which NF-κB-dependent metabolic mechanisms are core drivers of disease, in which cells they operate, and how they are influenced by the environment in specific disease states remain to be thoroughly documented. Another important question relates to how these mechanisms are transcriptionally regulated by NF-κB. In the future, it will be essential to methodically catalog the full spectrum of NF-κB-driven metabolic programs that contribute to tissue homeostasis and pathological states. It will be especially important to characterize the tissue- and context-specific dimensions of these programs and their precise contributions to distinct etiopathogenic processes. While this will prove to be a painstaking endeavor, it will enable future research to begin to realize the full diagnostic and therapeutic potential embodied in the NF-κB pathway. While it is not possible to predict how effectively this new knowledge will translate into novel diagnostics and therapeutics without thorough clinical investigations, the current data seem to provide a fertile ground for future explorations.

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Outstanding questions

Does NF-κB contribute to the metabolic adaptation of selected GC B cell populations to the hypoxic LZ microenvironment, especially since NF-κB and hypoxia inducible factor 1α (HIF-1α) pathways have been shown to engage in a mutual crosstalk in other tissues?

Further to the previous question, do the RelA and NF-κB2/p52 subunits contribute to terminal B cell differentiation in part by reprogramming cell metabolism, in addition to their established roles in upregulating *Irf4* and *Prdm1*(*Blimp1)* expression, given that PC-fated GC B cells must increase endoplasmic reticulum biogenesis and amino acid and glucose metabolism to sustain the secretion of massive amounts of antibodies by fueling protein synthesis and glycosylation? Furthering the molecular understanding of the metabolic functions of NF-κB in GC B cell differentiation and PC formation may lead to the development of novel strategies to potentially improve vaccine design and the management of patients with B cell lymphomas and autoimmune diseases.

Does NF-κB contribute to hematopoiesis and the maintenance of long-lived memory B cells by controlling stem cell metabolism, considering that FAO and OXPHOS are required to support stem cell renewal? Answering this question may help to develop better treatments for bone marrow hypoplastic conditions and extend duration of vaccine efficacy.

Does NF-κB signaling contribute to a reprogramming towards oxidative metabolism that promotes stemness and the epithelial-to-mesenchymal transition (EMT) in metastasis-prone cancers (given the pivotal role of NF-κB in driving tumor-based inflammation and the EMT, and the importance of FAO and OXPHOS in fueling increased cancer cell stemness in aggressive mesenchymal tumors, tumor cell survival following loss of attachment to the extracellular matrix, and metastatic dissemination)? Further, which downstream effectors are essential to mediating these NF-κB metabolic activities in cancer? A better understanding of the role(s) of NF-κB in these processes may guide the development of novel diagnostics and therapeutics for the improved treatment of patients with particularly aggressive tumors.

Declaration of interests

No interests are declared.

Resources

[i]www.bu.edu/nf-kb/gene-resources/target-genes/

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Although a deeper mechanistic understanding of NF-κB metabolic functions in immunity and oncogenesis can reveal potential vulnerabilities for therapeutic intervention, might this knowledge ultimately translate into tangible healthcare benefits? Working towards this will require the careful design of clinical studies and the development not only of rational drug discovery strategies but also of robust predictive biomarkers for patient stratification; these must account for disease biology as well as environmental states.

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