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Epigenetic and transcriptional regulation of innate immunity in cancer

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Abstract

Innate immune cells participate in the detection of tumor cells via complex signaling pathways mediated by pattern-recognition receptors, such as Toll-like receptors (TLR) and NOD-like receptors (NLR). These pathways are finely tuned via multiple mechanisms, including epigenetic regulation. It is well established that hematopoietic progenitors generate innate immune cells that can regulate cancer cell behavior, and the disruption of normal hematopoiesis in pathologic states may lead to altered immunity and the development of cancer. In this review, we discuss the epigenetic and transcriptional mechanisms that underlie the initiation and amplification of innate immune signaling in cancer. We also discuss new targeting possibilities for cancer control that exploit innate immune cells and signaling molecules, potentially heralding the next generation of immunotherapy.

Introduction

Host immunity can be classified into innate immunity, which is rapid to develop but less specific, and adaptive immunity, which is slower to develop but more specific. Innate immunity plays an important role in host defense against infection and cancer, recognizing various antigens via pattern recognition receptors (PRRs). Innate immune cells comprise a wide range of myeloid and lymphoid cell types that share common hematopoietic origin (1). Two major conceptual advances have highlighted our rapidly evolving understanding of innate immunity. First, bone marrow hematopoietic stem and progenitor cells (HSPCs) can sense systemic inflammation and adapt by increasing their proliferation rate and skewing differentiation toward myeloid cells. Such HSPC adaptations are beneficial in eliminating pathogens during the acute phase of infection. However, they may contribute to chronic inflammation, and to HSPC malfunction and exhaustion when sustained (2). Second, innate

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immune cells and HSPCs can exhibit adaptive characteristics, termed trained immunity; previous exposure to a pathogen leads to an enhanced innate immune response upon re-challenge (3). In this review, we focus on the epigenetic and transcriptional regulation of innate immune cells and signaling in different cancers. Also, we summarize how targeting innate immunity can spur the development of next generation cancer immunotherapies.

Regulation of the genesis of innate immune cells

Hematopoietic stem and progenitor cells (HSPC)—HSPCs generate a variety of cells that participate in innate immunity. Interferons (IFNs) play an important role in the response of HSPCs to inflammation. Activation of the type 1 IFN signaling pathway, mediated by IFN-α/β receptor IFNAR, drives the proliferation of dormant HSCs(4) while its inhibition, such as by the negative regulator, Irf2, promotes HSC quiescence(5). Additional mechanisms against IFN-α-induced HSC dysfunction include retinoic acid signaling(6), and the circular RNA cia-cGAS that antagonizes cyclic GMP-AMP (cGAMP) synthase cGAS-mediated virus DNA sensing(7). The effects of IFN-γ on HSCs are context-dependent. For example, HSC proliferation is promoted by IFN-γ-STAT1 signaling in response to mycobacterium infection(8). However, upon lymphocytic choriomeningitis virus infection, IFN-γ inhibits the proliferation of HSCs by reducing STAT5 phosphorylation (9). IFN-γ also induces myeloid differentiation dependent on Batf2 activity (10). TNF induces HSC proliferation and myeloid lineage differentiation by upregulating PU.1 (11). IL-3, produced by innate response activator B cells, induces myelopoiesis (12). The IL-6/IL-12 cytokine family members, including IL-27, also act on HSPCs to promote emergency myelopoiesis(13, 14). IL-1 directly accelerates cell division and myeloid differentiation by activating a PU.1-dependent gene program(15). This allows for rapid myeloid recovery following acute marrow injury; however, chronic IL-1 exposure compromises HSC self-renewal and restricts HSC lineage output (15).

Neutrophils—The generation of neutrophils from HSCs is regulated by a number of transcription factors (TFs), including C/EBPs, GATA-1, and PU.1. C/EBP-α induces early myeloid precursors to differentiate by negatively regulating the expression of c-Myc, via an E2F binding site in the c-Myc promoter(16). Then, the acetylation of C/EBP-ε at K121 and K198, together with the absence of GATA-1, triggers CMPs to commit to terminal neutrophil differentiation (17). PU.1 recruits HDAC1 to inhibit the accessibility of AP-1 binding motifs, thereby preventing the hyperactivation of neutrophils(18). AP-1 is a heterodimeric TF that is activated by inflammatory cytokines, growth factors, and infection, which activate kinases that modulate its transcriptional activity(19). AP-1 cooperates with other TFs, including NF-kB and IRF to stimulate the expression of type I IFNs and pro-inflammatory cytokines(20).

Our understanding of the roles that neutrophils play in cancer is growing. The prognostic value of circulating neutrophils and tumor-associated neutrophils have been assessed in various cancers (21). Anti-tumor (N1) and pro-tumor (N2) sub-populations of neutrophils have been identified(22). N1 are characterized by an immunostimulatory profile ($TNF\alpha^{high}$, $CCL3^{high}$, $ICAM\text{-}1^{high}$, $Arginase^{low}$) and cytotoxic activity towards tumor cells, whereas N2 exhibit upregulation of chemokine production (CCL2, 3, 4, 8, 12, and 17, and CXCL1, 2,

8 and 16)(23). The fate switch between N1 and N2 is controlled by transforming growth factor β (TGFβ) which promotes the N2 phenotype(24), and IFNβ which promotes the N1 phenotype(25). TGF-β signaling is transduced via SMAD proteins that regulate chromatin remodeling and transcription, either by direct DNA binding or indirectly through other TFs (26). IFNβ signaling is mediated by the activator of transcription (STAT) family of TFs (27). However, the epigenetic mechanisms that regulate cytokine and chemokine gene expression in neutrophils, in response to TGFβ or IFNβ, remains to be determined.

Macrophages—Macrophages phagocytize microorganisms and apoptotic cells, and produce inflammatory cytokines (28). Tissue-resident macrophages are established during embryonic and fetal hematopoiesis, but they can also arise from circulating monocytes after local macrophage depletion, inflammation, and normal aging (29). Regardless of their cell of origin, the major regulator of the macrophage lineage is the colony stimulating factor (CSF) 1 receptor (30). Expression of MafB and c-Maf also play a role in driving terminal macrophage differentiation(31). Moreover, the NAD-dependent lysine deacetylases, Sirtuins 1 and 2, play a critical role in macrophage differentiation via a direct interaction with DNMT3B (32). Notably, tumor-associated macrophages (TAMs) are mostly pro-tumorigenic in solid tumors, functioning to promote carcinogenesis, neoangiogenesis, immune-suppressive TME, chemoresistance, and metastasis. Reprogramming of immune-suppressive TAMs by pharmacological approaches has gathered much interest in recent years to improve cancer therapies (33).

Macrophages can be classified into M1 (classically activated macrophages, or kill-type macrophages) that are primed by Th1 cytokines such as IFN-γ and bacterial products, and M2 (alternatively activated macrophages, or repair-type macrophages) that are primed by Th2 cytokines such as IL-4 and IL-13 (34). IFN-γ plays a pivotal role in promoting immunity against cancer (35). IFN-γ triggers the receptor association of the JAK1 and JAK2 tyrosine kinases, which then induce the phosphorylation of STAT1 and STAT2. This promotes the binding of STAT1 homodimers to consensus DNA sequences termed GAS elements, triggering the expression of IFN-stimulated genes(36). In contrast, IFN-α leads to phosphorylation of STAT1 and STAT2, which heterodimerize and bind to an IFN-stimulated response element (ISRE) in conjunction with IRF9 (37). M1 macrophages elicit rapid pro-inflammatory responses to infection and tissue damage by sensing lipopolysaccharide and damage-associated molecular patterns, respectively, while M2 macrophages possess anti-inflammatory activities that enable these cells to resolve inflammation and promote tissue repair (38).

Epigenetic mechanisms that control macrophage polarization are being uncovered. M1 polarization, which can be driven by LPS and IFN- γ, requires dynamic metabolic reprogramming and a two-stage remodeling of the TCA cycle, including the transient accumulation and subsequent decrease in metabolites such as succinate and itaconate(39). The tumor environment provides signals such as PGE2 or TGF-β that inhibit M1 activation, thus M2 macrophages predominate in most human cancers, where they produce growth-promoting molecules for tumors(40). Jmjd3 (Jumonji domain-containing protein D3), a key H3K27 demethylase, whose activity is dependent on glutamine metabolism, controls M2 macrophage activation(41, 42); the production of α-ketoglutarate via glutaminolysis

promotes M2 macrophage activation via fatty acid oxidation and the Jmjd3-dependent epigenetic reprogramming of M2 genes(43). IL-4-induced M2 polarization of liver macrophages is dependent on the activation of STAT6-JMJD3 signaling and suppression of TLR4-NF-κB signaling(44). Macrophage heterogeneity is not fully represented by a dichotomy between M1 and M2. Macrophages also exhibit intermediate phenotypes and are in fact a continuum of polarization states from the two ends marked by M1 and M2. Heterogeneous subpopulations of macrophages take on a variety of roles depending on tissue type and the specific pathology (45). Macrophages even show plasticity after polarization (46). Thus, altering macrophage polarization dynamics, such as triggering an M2 to M1 macrophage transition, could slow or stop cancer growth, a strategy that form the basis for novel cancer immunotherapy (40).

Myeloid-derived suppressor cells (MDSCs)—MDSCs are cells of myeloid origin with potent immune-suppressive functions(47). MDSC generation occurs in two phases in cancer, an expansion phase driven mainly by tumor-derived growth factors that promote the accumulation of immature myeloid cells, and an activation phase driven mainly by tumor stroma-derived proinflammatory cytokines, which convert immature myeloid cells into MDSCs(48). A complex network of extracellular signals, chromatin modulators, and TFs is involved in the regulation of MDSCs. For example, the increased production of IL-6 in mouse myeloid cells results in STAT3 activation and MDSC expansion(49). Hypoxia-inducible factor (HIF)-1α positively regulates the VISTA (V-domain Ig suppressor of T-cell activation) promoter, increasing VISTA expression on myeloid cells and facilitating MDSC-mediated suppression of T-cell activity(50). DNMT3A downregulation erases MDSC-specific hypermethylation and abolishes their immunosuppressive capacity in cancer(51). Moreover, NLRP3 is expressed in MDSCs (52); Nlrp3-deficient mice exhibit decreased MDSCs at the tumor site, implicating NLRP3 in MDSC expansion and/or recruitment (53).

The epigenetic regulation of the generation of different MDSC subsets is being defined. STAT3 signaling, induced by various soluble mediators, is required for Mo-MDSC generation (54). The IFN-γ-STAT1-IRF1 axis appears to be specifically crucial for Mo-MDSC suppressive activity (55). In contrast, the generation of human G-MDSCs is less clear. These cells are morphologically heterogeneous, ranging in appearance from immature to mature neutrophils (56), and recent studies suggest that immunosuppressive G-MDSCs can be derived from mature neutrophils(57). STAT3 can also trigger PMN-MDSC accumulation by increasing the expression of several components of the NADPH complex, such as S100A9, that leads to increased ROS production (58). IRF-8 limits MDSC generation, particularly the PMN-MDSC subset, in mouse mammary tumor models (59). The biology and regulatory mechanisms of MDSC subsets need further characterization.

Innate lymphoid cells (ILCs) and dendritic cells (DCs)—ILCs and DCs also contribute to the innate arm of the immune system. ILCs are a heterogeneous group of cells that derive from common lymphoid progenitors but lack rearranged antigen receptor genes. Five classes of ILCs (NK cells, ILC1, ILC2, ILC3, and lymphoid tissue-inducer cells) have been defined based on differences in TF expression and their cytokine production. We

refer readers to two recent reviews that comprehensively cover the roles of NK cells and other ILCs in cancer(60, 61).

DCs represent a heterogeneous family of immune cells that bridge innate and adaptive immunity, as impaired DC activation, licensing, or maturation also compromises antigen-specific T cell immunity. The importance of DC biology in anti-tumor immunity has gained attention recently. DC-based anti-tumor vaccines have been FDA-approved for treating prostate cancer, while similar and other approaches are begin studied and assessed in clinical trials. Given space constraints, we refer readers to two recent reviews that cover this growing field (62, 63).

Innate immune signaling in cancer

PRRs mediate innate immune signaling and can be classified based on their subcellular localizations: membrane-bound receptors, including Toll-like receptors (TLRs) and C-type lectin receptors (CLRs), and intracellular receptors, including NOD-like receptors (NLRs), AIM2-like receptors (ALRs), and RIG-I-like receptors (RLRs) (64). Upon recognition of “non-self” antigens, the innate immune system responds by producing cytokines, chemokines and IFNs, and by activating phagocytosis, autophagy, and cell death (Figure 1).

Toll-like receptors (TLRs)—TLRs are expressed in antigen-presenting cells (APCs) and other immune cell types including mast cells, NK cells, regulatory T cells, monocytes, neutrophils and basophils (65). TLRs are also expressed by tumor cells, where they play anti- or pro-tumor roles depending on cell context(66). Upon ligand binding, the TLRs dimerize and signal through different sets of adaptor proteins, including (a) TIRAP/MyD88, the TIR-containing adaptor protein (TIRAP) and the protein myeloid differentiation primary response 88 (MyD88), (b) TRAM/TRIF, the TIR domain–containing adaptor-inducing IFN-β (TRIF) and the TRIF-related adaptor molecule (TRAM), (c) MAVS, the mitochondrial antiviral signaling protein, and (d) ASCs, Apoptosis-associated speck-like proteins containing a CARD (caspase recruitment domain), which allow for different transcriptional outputs (64).

Intriguingly, TLRs are also expressed by HSPCs. TLR ligand binding blocks HSPC expansion(67) and induces myeloid differentiation in a MyD88-dependent manner (68). The activation of TLRs in ST-HSCs and MPPs also results in substantial cytokine production via activation of NF-κB. Loss of TLR signaling enhances HSC repopulating capacity, as HSCs from Tlr2−/−, Tlr4−/−, Tlr9−/−, or MyD88−/− mice show an advantage over normal HSCs (69, 70). Similarly, TLR activation leads to compromised self-renewal and HSPC exhaustion, mediated by TRIF, rather than MyD88, with the production of ROS and activation of the MAPK p38, leading to replication stress(71, 72). These findings highlight the role of TLR signaling in regulating the behavior of HSPCs, cancer cells, and host defense.

Aberrant TLR signaling is also linked to malignant hematopoiesis. Overexpression of TLR genes in HSCs may contribute to the pathogenesis of myelodysplastic syndrome (MDS) (73). A recent study of 149 MDS patients showed that TLR1, TLR2 and TLR6 and multiple

TLR downstream genes are significantly overexpressed in CD34+ MDS bone marrow cells(74). TLR signaling is promoted by several bromodomain and extra-terminal (BET) proteins, which bind to acetylated proteins including histones H3 and H4, and promote tumor growth in several lymphoma models (75). BET inhibitors suppress the expression of TLR2/4 and the transcription of IL-1β, IL-6, and TNF-α and thus may have anti-tumor activity(76).

NOD-like receptors (NLRs) and the inflammasome—NLRs are cytoplasmic receptors that mediate the innate immune response(77). Members of the NLR family of PRRs possess a C-terminal leucine-rich repeat (LRR) domain, a central nucleotide binding domain (NBD), and a distinct N-terminal domain that differs between subfamilies(78). The two most prominent NLR subfamilies have either a pyrin domain (PYD) at their N-terminus, or one or more caspase recruitment (CARD) domains(79). Upon sensing pathogens or host derived proteins, NLRs oligomerize and assemble the inflammasome, which serves as a caspase-1-activating scaffold to activate the proinflammatory IL-1 family of cytokines, IL-1β and IL-18, triggering a specific type of inflammatory cell death, termed pyroptosis(80). NLR-inflammasome pathways have been linked to both solid tumors and hematological malignancies (81, 82).

Priming signals are required for the expression of inflammasome components, which can be induced by TLR ligands, or via the TNF or IL-1β signaling pathways that lead to NF-κB activation (83). Hypomethylation of CpG sites within other inflammasome genes such as NLRC4 and NLRP12, and IL-1β has been associated with upregulation of their expression in Kawasaki disease(84). Furthermore, increased expression of CtBPs (C-terminal-binding proteins), together with p300 and AP-1, activates NLRP3 expression, which aggravates the inflammatory response in osteoarthritis(85). Histone deacetylase 6 (HDAC6), inhibits the activation of the NLRP3 inflammasome in mouse bone marrow-derived macrophages by directly associating with ubiquitinated NLRP3 through its ubiquitin-binding domain (86). Inflammasomes also regulate hematopoiesis and the generation of innate immune cells; loss of inflammasome components or caspase-1 inhibition inhibits myelopoiesis, in a GATA1-dependent manner(87). The impact of crosstalk between epigenetic modifiers and the various NLR-inflammasome pathways is largely unknown in specific cancers.

C-type lectin receptors (CLRs), RIG-I-like receptors (RLRs), and AIM2-like receptors (ALRs)—CLRs, characterized by C-type lectin-like domains, form a large heterogeneous group of transmembrane and soluble receptors(88). The roles of CLRs in immunity and cancer are being delineated and were recently reviewed(89, 90). However, little is known about the epigenetic regulation of CLR generation or function. The TF NFATc2 activates the expression of specific cytokines and chemokines in DCs in response to CLR dectin-1 stimulation, and induces the H3K4 trimethylation that is associated with enhanced gene expression(91). Manipulation, i.e. a decrease in the activity of the histone lysine-methyltransferase Ezh2 increases the generation of IL-15R(+) CD122(+) NK precursors and mature NK progeny from mouse and human HSPCs(92). The enhanced NK cell expansion and cytotoxicity against tumor cells are associated with the up-regulation of both CD122 and the CLR NKG2D(92).

RLRs induce the transcription of type I IFNs and other genes by sensing viral and host-derived RNAs. The regulatory mechanisms that control the generation of RLRs, their roles in viral infection, autoimmunity, and cancer, and their therapeutic potential, have recently been reviewed(93). ALRs represent a newly recognized class of PRRs that function in cytosolic and nuclear pathogen DNA sensing. ALRs recruit ASC and caspase-1 to form inflammasomes, which elicit inflammatory responses by producing IL-1β and IL-18, and by triggering pyroptosis (94). The epigenetic regulation of ALRs is yet to be studied.

Trained immunity in cancer

Transcriptional and epigenetic reprogramming—The molecular basis of trained immunity is only partially understood, but it is clearly regulated by transcriptional and epigenetic reprogramming, involving chromatin organization at the level of the topologically associated domains (TADs), long non-coding RNAs, and reprogramming of cellular metabolism (Figure 2)(95, 96). Trained immunity occurs in part via the epigenetic regulation of the monocyte-to-macrophage differentiation transition, where roughly equal numbers of promoters are turned on or off (97). Furthermore, DNA methylation patterns in peripheral blood mononuclear cells can also reflect their capability of undergoing trained immunity(98, 99). During adaptive NK cell responses, specific TFs promote permissive histone modifications and chromatin accessibility, including RUNX family members, STAT family members, IRF8, IRF9, KLF12, and T-box TFs(100–105).

Trained immunity also occurs within HSPCs. For example, exposure to β-glucans, which are fungal cell wall polysaccharides, promotes the expansion of myeloid progenitors and increases innate immune signaling in mice(106). Likewise, BCG (Bacille Calmette-Guérin), an attenuated version of Mycobacterium bovis, increases the chromatin openness of specific TADs in mouse HSCs (107). Intriguingly, inflammasomes promote trained immunity at the level of HSPCs. Transcriptomic and epigenomic reprogramming induced by a high-fat diet is dependent on NLRP3(108). Recently, trained immunity that occurs in HSPCs is termed central trained immunity, which in part explains the long-lasting phenotype of trained immunity (96).

Immunometabolism and inflammaging—Metabolic intermediates can function as signaling nodes, substrates, co-factors, or inhibitors for chromatin-modifying enzymes(109). Trained monocytes show increased glycolysis, which is dependent on activation of mTOR through the dectin-1/Akt/HIF1α pathway(110). Subsequent studies show that glycolysis, glutaminolysis, and the cholesterol synthesis pathway are essential for the induction of trained immunity in monocytes(111, 112). Accumulation of fumarate induces the epigenetic reprogramming of monocytes by inhibiting KDM5 histone demethylases(111), while mevalonate, an intermediate in the cholesterol synthesis pathway, contributes to the training of human monocytes, via activation of IGF1-R and mTOR and via subsequent histone modifications in inflammatory pathways(113). These findings indicate that rewiring of cellular metabolism toward aerobic glycolysis and cholesterol synthesis may be integral to trained immunity.

How metabolic changes affect trained immunity in cancer is not well characterized. However, chronic, sterile, low-grade inflammation, termed inflammaging, has been studied in age-related diseases, including cancer(114). Clonal hematopoiesis of indeterminate potential (CHIP), more common in the elderly, is associated with an increased risk of developing myeloid malignancies and atherosclerosis (115, 116). Individuals with CHIP frequently have mutations in epigenetic modifiers such as DNMT3A, TET2, or ASXL1. Intriguingly, Tet2-deficient HSPCs demonstrate clonal expansion and accelerate atherosclerosis in mice, in a NLRP3 inflammasome/IL-1β pathway-dependent manner(117). Circulating monocytes of patients with atherosclerosis exhibit enhanced cytokine production and glycolytic metabolism, with epigenetic reprogramming at the level of histone methylation(118, 119). These findings highlight the role of metabolic and epigenetic changes in aging and age-related diseases. Further studies are needed to dissect the links between metabolic and epigenetic remodeling, trained immunity, aging, and cancer.

Targeting innate immunity: next generation of cancer immunotherapy

The current, FDA-approved immunotherapies for cancer rely largely on the adaptive immune system. However, advances in our understanding of innate immunity provide a novel framework for targeting this aspect of immune homeostasis to maintain health and prevent disease (Table 1). β-glucans and BCG have been evaluated in a variety of cancers, including neuroblastoma, bladder cancer, and lung cancer (120, 121). The protective effect of BCG vaccine relies on trained immunity, specifically the epigenetic reprogramming of monocytes at the level of H3K4m3 (122). Similarly, β-glucans induce trained immunity at the HSPC level and promote myeloid differentiation, innate immune signaling, and metabolic adaptations(106). β-glucans, given in combination with cetuximab in patients with KRAS-mutant colorectal cancer, have promising clinical activity in a phase II trial(123). While increases in the histone marks H3K4me3 and H3K9me3 underlie both BCG-induced and β-glucan-induced trained immunity(111, 112, 124), how this control trained immunity is unclear.

The synthetic peptide conjugate muramyl dipeptide (MDP), a peptidoglycan minimal bioactive motif common to all bacteria, activates innate immune cells through NOD2, activating NF-κB and inducing epigenetic rewiring and trained immunity (125). The ketone metabolite β-hydroxybutyrate and the small-molecule inhibitor MCC950 can inhibit NLRP3 inflammasome-mediated trained immunity(108, 126–128). Combinatorial use of epigenetic drugs with immunotherapy are also being investigated. For example, DNMT inhibitor 5-azacytidine triggers immune response via dsRNA sensing pathway, sensitizing melanoma cells to anti-CTLA4 therapy(129).

TLR agonists are being exploited as adjuvants for cancer vaccines as well as direct cancer therapeutics. Imiquimod binds to TLR7 to reverse local immunosuppression and induce skin cancer cell apoptosis (130). Flagellin fusion proteins can induce specific immune responses, mediated by TLR5 activation on target APCs (131). CpG oligo-deoxynucleotides, which are TLR9 agonists, have shown promising results as vaccine adjuvants and when used in combination with cancer immunotherapy(132). Polyriboinosinic-polyribocytidylic

acid (poly(I:C)), which targets TLR3 and TLR9, can boost immune system activation and promote anti-cancer effects (133).

Given the established track record of kinase inhibitors being approved to treat cancer, and other disorders, inhibitors of the kinases involved in innate immunity are being studied. IRAK functions downstream of TLRs and IL-1R to regulate the expression of inflammatory molecules. These kinases play a pro-tumor roles in several cancers (134): For example, inhibition of IRAK1/4 synergizes with sorafenib in suppressing the growth of hepatocellular carcinoma in a xenograft mouse model(135), while the combination of IRAK1/4 inhibition and lenvatinib decreases tumor volume in a mouse anaplastic thyroid cancer model, better than either therapy alone(136). A multikinase FLT3-IRAK1/4 inhibitor displays superior efficacy, compared to current FLT3-targeted therapies to eliminate adaptive resistance of FLT3-mutant AML (137). Other kinase inhibitors, such as those targeting TAK1 kinase, which is downstream of TLR and TNFR pathways, also show therapeutic efficacy in various cancer models(138–140). Taken together, kinase inhibitors and other drugs that target aspects of innate immunity, such as the cGAS-STING pathway or macrophage checkpoints (CD47/SIRPα axis) show important promise. Several of these approaches have recently been reviewed(141, 142).

Perspectives

The study of innate immunity in cancer is fast growing and drugs that target pro-tumorigenic cellular infiltration or inflammation are being tested preclinically and clinically. However, multiple challenges exist, given the complexity of the interactions between tumor cells and their environment and the importance of targeting only certain aspects of the immune system, without impairing others. On the molecular level, a better understanding of the mechanistic details underlying the intricate interactions between cancer biology, innate immunity signaling, and inflammation is needed. Clearly, the effects of feedback and compensatory pathways on tumor growth are hard to predict or control, despite the research advances we have outlined above. On the cellular level, the heterogeneity and plasticity of the immune cells that infiltrate tumors must be taken into account in cancer to target the biology of a specific immune cell type or the interactions between cell types. Also, the roles that aging or the microbiome has on the outcome of anti-inflammatory therapies remain to be characterized(143).

Notably, trained immunity provides a compelling layer of control on myeloid cell function by integrating epigenetic, transcriptional, and metabolic regulations, although the precise mechanisms are just beginning to be discovered. The presence of persistent epigenetic marks in trained innate immune cells, generated following a pathological process or during aging, could underlie an increased susceptibility to certain cancer events. Innate immunity can be therapeutically manipulated, at the level of epigenetic modifiers, TFs, cellular metabolism and signaling pathways. Moreover, mediators of innate immunity such as IFNs and cytokines can enhance adaptive immunity-based therapy by sensitizing tumor cells(144, 145). Mechanistic studies of innate immunity regulation in cancer are underway, which will help lay the groundwork for the development of innate immunity-based mono- or combination therapies.

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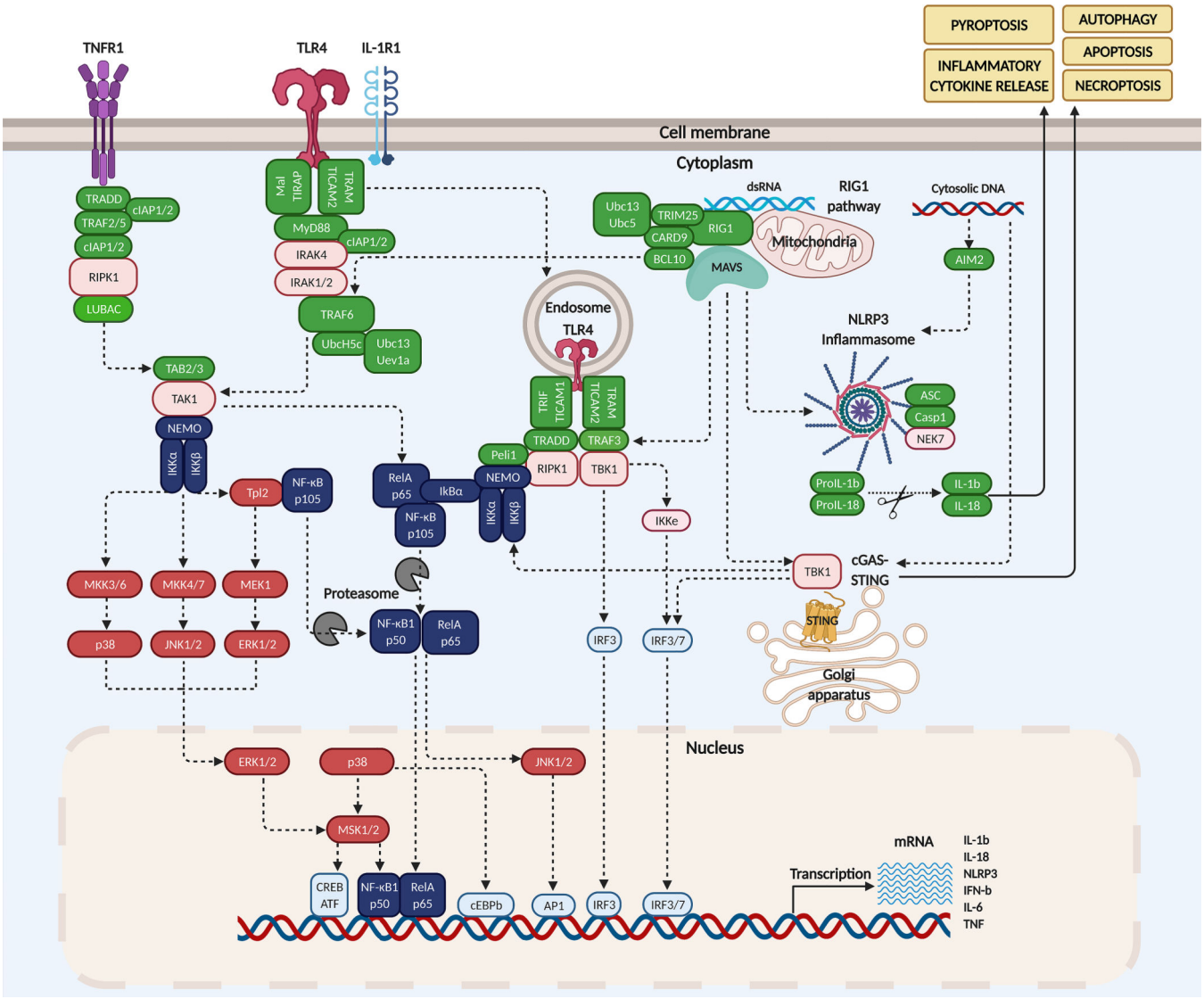

Figure 1. Innate immune signaling pathways

TNF binding to TNFR1 triggers the assembly of LUBAC ssscomplex, and the activation of TAK1 and subsequently IKK. TLR4 or IL-1R1 triggers the interaction of the MyD88-IRAK complex which engages TRAF6. Activated TLR4 can also be endocytosed and signal via RIPK1. RIG1 binding to dsRNA promotes its association to MAVS complex which converges on TRAF6. MAVS also interacts with TRAF3, TBK1, and STING to activate IRF3 and IRF7. NLRP3 triggers secretion of IL-1b and IL-18.

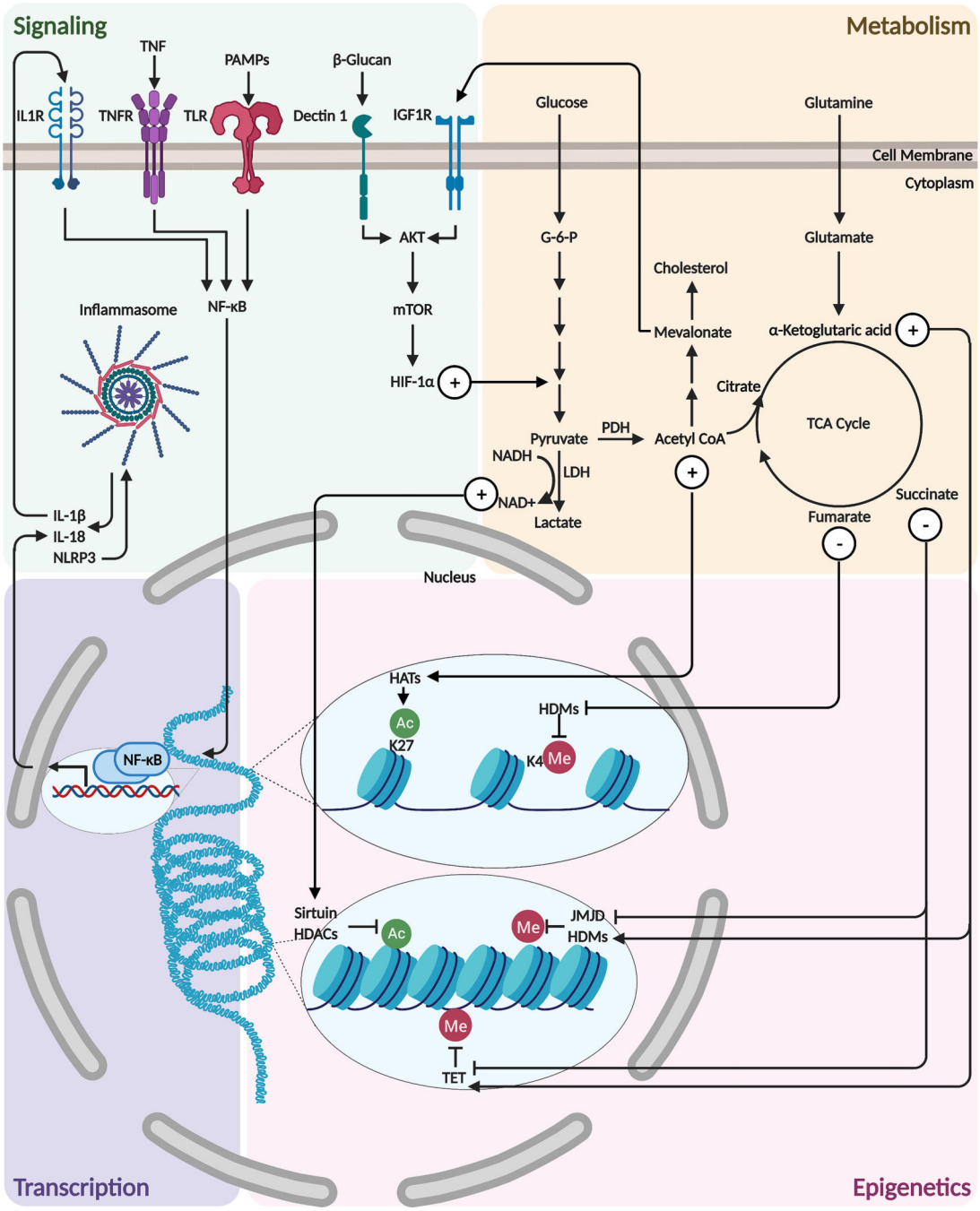

Figure 2. Trained immunity

Challenge of innate immune cells and HSPCs with training stimuli induces changes in cell signaling and metabolism. Specific TFs, such as NF-κB or AP-1, and epigenetic enzymes, induce chromatin and DNA modifications, and regulate gene transcription. Expression of these genes in turn feeds the machinery of innate immunity and promotes cytokine secretion.

Table 1.

Immunotherapies in cancer

Drugs	Targets	Effect on Epigenetics or Biology
Targeting Trained Immunotherapy		
BCG vaccine	Mycobacterium Tuberculosis	H3K4 trimethylation of monocytes
B-glucans	Dectin-1 and complement receptor 3 (CR3)	H3K4 and H3K9 trimethylation
Muramyl dipeptide (MDP)	NOD2	Activate NF-κB pathway
Statins	Mevalonate	Change DNA methylation and prevent trained immunity induction
B-hydroxybutyrate and MCC950	NLRP3	Inhibit NLRP3 inflammasome-mediated trained immunity
Targeting Innate Immune Signaling		
CpG oligo-deoxynucleotides (ODNs)	TLR9	Active innate immune responses by producing pro-inflammation cytokines and Th1 the helper-T cells
Imiquimod	TLR7	Reverse local immunosuppression and induce tumor cell specific apoptosis
Polyriboinosinic-polyribocytidylic acid (poly(I:C))	TLR9 TLR3	Induce stable maturation of functionally active dendritic cells Induce cancer cell apoptosis
Flagellin-protein fusions	TLR5	Induces inflammatory responses through the activation of antigen-presenting cells
IRAK1/4 Inhibitor I	IRAK1/4	Suppresses solid tumor growth in several distinct combination therapies
NCGC1481	FLT3-IRAK1/4	Eliminates adaptive resistance of FLT3-mutant AML cells
NG25	TAK1	Inhibits colorectal cancer cell proliferation, especially for KRAS-mutant cells
5Z-7-oxozeaenol	TAK1	Enhances the sensitivity of glioblastoma cells to chemotherapy Suppresses triple-negative breast cancer metastasis by altering TAK1-p38 signaling
C-178, C-176	STING	Inhibits STING palmitoylation and attenuates autoinflammatory features in mice
NCGC00138783, Pep-20, etc	CD47/SIRPα	Small-molecule inhibitors targeting macrophage checkpoints that induce phagocytosis