Review

The CB_2 Receptor in Immune Regulation and Disease: Genetic Architecture, Epigenetic Control, and Emerging Therapeutic Strategies

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Review

The CB_2 Receptor in Immune Regulation and Disease: Genetic Architecture, Epigenetic Control, and Emerging Therapeutic Strategies

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Abstract

The cannabinoid receptor type 2 (CB_2) is gaining recognition as a critical regulator of immune equilibrium, neuroinflammation, and tissue repair processes. Unlike its counterpart, the CB_1 receptor, which produces psychoactive effects when activated, the CB_2 receptor presents itself as a more appealing and safer target for therapeutic interventions. This review investigates the genetic and epigenetic regulation of CB_2 receptor and examines how its signaling affects both immune and nervous system cells. We emphasize its influence on microglial activity, the modulation of immune responses, and its regulation by non-coding RNAs and chromatin remodeling. Through these pathways, CB_2 receptor plays a significant role in various disease processes, with increasing evidence connecting it to depression, chronic pain, schizophrenia, inflammatory conditions such as asthma and colitis, and even cancer immunotherapy. We also explore how CB_2 receptor interacts with components of the endocannabinoid system, including Transient Receptor Potential (TRP) channels, prostanoids, and Peroxisome proliferator-activated receptors (PPARs). Lastly, we analyze how innovative therapies targeting CB_2 receptor, such as selective agonists, positive allosteric modulators (PAMs), and biased ligands, could pave the way for more precise and effective treatments for neurological, inflammatory, and immune-related disorders.

Keywords: CB_2 receptor; immune modulation; endocannabinoidome; G Protein-Coupled Receptors (GPCRs); neuroinflammation; autoimmune disorders; epigenetic regulation; cannabinoid pharmacology; cancer immunotherapy; checkpoint modulation

Highlights

- CB_2 receptor signaling modulates inflammation, pain, and neuropsychiatric states.
- CB_2 receptor expression is inducible in immune and brain cells, regulated by epigenetic and transcriptional cues.
- CB_2 receptor activation influences microglial M1/M2 polarization and dampens neuroinflammation.
- CB_2 receptor is a promising target in schizophrenia, acting on dopaminergic and hippocampal circuits.
- CB_2 receptor agonists and PAMs show therapeutic potential in autoimmune and cancer contexts.
- Crosstalk exists between CB_2 receptor and other ECS components (TRPs, PPARs, prostanoids).
- Novel CB_2 receptor-selective drugs offer biased signaling and enhanced clinical specificity.

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1. Introduction

It is now accepted that the endocannabinoid system (ECS) is a sophisticated and evolutionarily preserved lipid signaling network that regulates various physiological and pathological processes, encompassing immune surveillance, inflammation, energy balance, emotional regulation, pain perception, and synaptic transmission[1]. Throughout history, cannabis has been utilized by ancient civilizations for its pain-relieving and therapeutic benefits[2]. However, it was only in the mid-20th century that the compounds derived from cannabis were identified structurally, leading to the discovery of Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD) as the primary active components of Cannabis sativa[3]. A pivotal advancement occurred with the uncovering of endogenous cannabinoids anandamide (*N*-arachidonoyl-ethanolamine; AEA) and 2-arachidonoyl-glycerol (2-AG), alongside their corresponding receptors, CB_1 receptor and CB_2 receptor, as well as the enzymes responsible for their synthesis and degradation, such as N-acyl phosphatidylethanolamine-specific phospholipase D (NAPE-PLD), diacylglycerol lipase (DAGLα/β), fatty acid amide hydrolase (FAAH), and monoacylglycerol lipase (MAGL)[4]. CB_1 receptors are highly represented in the central nervous system (CNS), primarily mediating the psychoactive effects of THC and regulating neurotransmitter release[5]. Conversely, CB_2 receptors were initially identified as peripheral receptors in immune tissues, such as the spleen, tonsils, and circulating leukocytes[6–8]. Nonetheless, growing evidence has shown that CB_2 receptors can also be inducibly expressed in the CNS during inflammatory or neuropathological conditions, particularly in microglia, astrocytes, and specific neuronal types[9]. This system functions as a precisely regulated homeostatic network activated as needed in response to stress, injury, or immune challenges[10].

CB_2 receptor has attracted significant interest due to its non-psychoactive characteristics and diverse immunomodulatory roles[11,12]. In basic and translational studies, researchers are actively investigating its functions in inflammation, immune cell movement, mood regulation, neurodegeneration, and cancer immunity[13–15]. As the understanding of CB_2 receptor dynamics deepens, including its inducible expression, cell-type specificity, and distinct signaling capabilities, there is growing interest in leveraging its potential for therapeutic intervention. Herein, we provide an in-depth analysis of CB_2 receptor biology, covering aspects from molecular structure and epigenetic regulation to its involvement in inflammation, neurodegeneration, mental health disorders, and immune checkpoint regulation in cancer. The review synthesizes mechanistic studies, knockout models, and pharmacological interventions to create a framework relevant to understanding CB_2 receptor as a therapeutic target within the larger endocannabinoidome (eCBome).

2. Molecular Biology of the CB_2 Receptor

The CB_2 receptor is encoded by the *CNR2* gene in humans, which is located on chromosome 1p36[16]. The typical isoform consists of a protein made up of 360 amino acids, featuring seven transmembrane α-helices that are typical of class A GPCRs, with an extracellular N-terminus that plays a role in ligand binding and an intracellular C-terminal domain essential for signaling and receptor transport[17]. The CB_2 receptor shares around 44% sequence homology with the CB_1 receptor but displays expression patterns and pharmacological characteristics that vary by tissue[18]. Notably, CB_2 receptor exhibits 82% sequence similarity between humans and rodents; however, there are species-specific differences in expression and function that must be considered when interpreting preclinical results[19]. CB_2 receptors act as context-sensitive signaling hubs, influenced by complex epigenetic, transcriptional, and post-translational regulatory mechanisms[20,21]. Their capability to variably interact with downstream effectors in a cell- and ligand-specific way makes them appealing targets for precision pharmacotherapy aimed at a range of immune, neurological, and psychiatric conditions[22]. Although present in low abundance in healthy CNS tissue, CB_2 receptor mRNA and protein expression increase significantly in microglia and specific neurons under inflammatory or neuropathological conditions. CB_2 receptor is highly prevalent in B lymphocytes within peripheral immune tissues, followed by NK cells, macrophages, and monocytes in these regions[23].

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Importantly, Simard et al. (2022) provided a comprehensive transcriptomic analysis of human peripheral leukocytes, revealing that CB2 receptor mRNA is significantly upregulated in granulocytes (neutrophils and eosinophils) and PBMCs (monocytes, B and T lymphocytes)[8]. This receptor can also be found in stem cells derived from bone marrow and various epithelial and endothelial tissues[24,25]. In the brain, the CB_2 receptor has been identified in regions such as the hippocampus, substantia nigra, cortex, amygdala, and prefrontal cortex, particularly during pathological condition[26].

3. Epigenetic and Transcriptional Regulation of the CB_2 Receptor

The regulation of the CNR2 gene through epigenetic processes is crucial for modulating CB_2 receptor expression in response to various environmental and cellular stimuli[27]. Different layers of epigenetic control, including DNA methylation, histone modifications, and non-coding RNAs, regulate the accessibility and transcriptional activity of the CNR2 region[16,28]. These processes not only calibrate receptor expression but also enable CB_2 receptor to adjust its immune and neuroinflammatory roles in line with physiological demands.

3.1. DNA Methylation and Transcriptional Silencing

A key mechanism influencing CB_2 receptor expression is the methylation of DNA at CpG-rich regions within the CNR2 promoter[29]. In the absence of inflammation, DNA methyltransferases (DNMT1, DNMT3A, and DNMT3B) add methyl groups to cytosines in these CpG islands[29–31]. This methylation inhibits gene transcription primarily through two means: (1) it directly obstructs transcription factor binding, and (2) it recruits methyl-CpG-binding proteins like MeCP2[29,32–34]. MeCP2 then acts as a platform to attract histone deacetylases (HDACs) and chromatin remodeling complexes, which compact the chromatin and maintain a transcriptionally inactive state[29,35]. This repression, however, is dynamic and can be reversed. Environmental factors, such as inflammation, infection, psychological stress, or exposure to cannabinoids, can trigger TET enzymes (TET1, TET2, and TET3), which convert 5-methylcytosine to 5-hydroxymethylcytosine[36,37]. This modification promotes a shift toward a more open chromatin state, creating a permissive environment for gene transcription, which may include reactivation of the CNR2 gene under appropriate cellular conditions[36]. Furthermore, activation-induced cytidine deaminase (AID) and members of the APOBEC family aid demethylation by initiating base excision repair pathways that restore unmethylated cytosines[29]. These adaptive epigenetic alterations enable rapid increases in CB_2 receptor expression in both immune and neural cells during inflammatory or pathological conditions[4].

3.2. Histone Modifications and Chromatin Accessibility

Histone modifications work synergistically with DNA methylation to finely regulate the chromatin environment surrounding the CNR2 gene[16]. Enhancing histone marks, such as acetylation of histone H3 at lysine 9 (H3K9ac) and trimethylation at lysine 4 (H3K4me3), are closely linked to open chromatin and active gene transcription[16,38,39]. These activating changes are facilitated by enzymes such as CBP/p300, a group of transcriptional coactivators crucial for regulating gene expression, and MLL family methyltransferases[40–44]. Their activity is frequently stimulated by pro-inflammatory signals, immune activation, or engagement of the CB_2 receptor, which kick-starts downstream signaling pathways such as MAPK/ERK and PI3K/Akt[30]. These pathways further enhance the recruitment of co-activators and transcription factors to the CNR2 promoter, boosting gene expression[27].[36,37]

Conversely, repressive histone marks, such as H3K9me2 and H3K27me3, are introduced by histone methyltransferases G9a and EZH2, respectively, the primary components of the Polycomb Repressive Complex 2 (PRC2)[30,45–47]. These modifications lead to chromatin compaction and transcriptional repression. The dynamic interplay between activating and repressive histone

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modifications ultimately decides whether CB_2 receptor remains inactive or is actively transcribed, enabling the receptor to respond accurately to shifting physiological conditions[48].

3.3. Non-Coding RNAs: MicroRNAs and Long Non-Coding RNAs

Non-coding RNAs add an additional layer of regulatory complexity to the expression of CB_2 receptor[30,49]. MicroRNAs (miRNAs), such as miR-139 and miR-665, have been identified as binders to the 3′ untranslated region (3′ UTR) of CNR2 mRNA, inhibiting translation under resting conditions[50–52]. In cases of chronic heart failure, there is a notable increase in CB_2 receptor expression within human heart muscle tissue, indicating a possible adaptive mechanism involving the endocannabinoid system. Weis et al. (2010) found that levels of CB_2 receptor mRNA were significantly elevated in the myocardium of left ventricular failure, while CB_1 receptor expression showed a slight decline. This shift in receptor expression was correlated with a considerable increase in circulating endocannabinoids, indicating an overall activation of the endocannabinoid system[53]. Similarly, Möhnle et al. (2014) demonstrated that miR-665 functions as a post-transcriptional regulator of the CB_2 receptor. Their research indicated that miR-665 was notably downregulated in heart tissue samples from patients with heart failure and was predicted, through bioinformatic analysis, to target the 3′ untranslated region of CNR2 mRNA. The negative correlation observed between miR-665 and CB_2 receptor expression suggests a regulatory mechanism in which lower levels of miR-665 may alleviate the translational inhibition of CB_2 receptor, thereby promoting increased receptor expression. Collectively, these results highlight a coordinated mechanism in which modulation of microRNA and heightened endocannabinoid activity may facilitate CB_2 receptor-mediated responses as a compensatory adaptation in the failing heart[54].

3.4. Pharmacological Modulation of the CB_2 receptor: Biased Agonism, Allosteric Control, and Post-Translational Regulation

When activated by endogenous ligands (AEA, 2-AG) or synthetic compounds (such as JWH-133), CB_2 receptors associate with Gαi/o proteins, leading to the inhibition of adenylyl cyclase, decreased cAMP synthesis, and subsequent suppression of PKA[55–57]. Beyond traditional G protein signaling, CB_2 receptors also interact with β-arrestin pathways, which are responsible for receptor internalization, desensitization, and alternative signaling routes, including ERK1/2, p38 MAPK, and PI3K/Akt[58,59]. Evidence of ligand-biased signaling has shown that different ligands can preferentially engage either G protein or β-arrestin pathways, allowing for pharmacological fine-tuning[60,61]. Allosteric modulation is an innovative strategy to enhance or inhibit CB_2 receptor activity selectively[62]. Positive allosteric modulators (PAMs), such as EC21a and endogenous peptides like Pepcan-12, increase the sensitivity of CB_2 receptors to endogenous cannabinoids without acting as direct agonists, thus preserving physiological signaling dynamics[62–64]. Conversely, negative allosteric modulators (NAMs) can diminish receptor activity and may provide therapeutic advantages in conditions involving excessive CB_2 receptor activation[65–67]. CB_2 receptors also undergo post-translational modifications, including glycosylation and phosphorylation, which influence receptor transport, localization, and the accuracy of signaling[68–70]. G protein-coupled receptor kinases (GRKs) and β-arrestins regulate receptor desensitization and recycling, while receptor dimerization with CB_1 receptor or other GPCRs introduces another layer of functional complexity[71,72].

4. The Role of CB_2 Receptor in Immune Regulation

The CB_2 receptor serves as a crucial modulator of immune homeostasis, influencing both innate and adaptive immune responses through mechanisms that are specific to different cells and contexts[73]. It is highly expressed in the hematopoietic system and is essential for leukocyte activation, production of cytokines, cell migration, and infiltration into tissues[74]. In contrast to the CB_1 receptor, which has limited expression in immune cells, the CB_2 receptor has strong expression.

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It can be induced by inflammatory signals, making it a key therapeutic target for inflammatory and autoimmune disorders[75].

The activation of the CB_2 receptor results in the inhibition of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, IL-6, and interferon-gamma (IFN-γ), while it encourages the production of anti-inflammatory cytokines, including IL-10 and transforming growth factor-beta (TGF-β)[76–78]. This shift in cytokine profiles is achieved through the inhibition of NF-κB signaling, decreased cAMP levels, and reduced activity of MAPK pathways[79,80]. Additionally, CB_2 receptor influences inflammasome activation and the generation of reactive oxygen species (ROS), which contributes to its anti-inflammatory characteristics[81].

CB_2 receptor signaling promotes the M2 anti-inflammatory phenotype in monocytes and macrophages over the M1 pro-inflammatory state[11,82]. This polarization is driven by transcription factors, such as signal transducer and activator of transcription 6 (STAT6), and nuclear receptors, including peroxisome proliferator-activated receptor (PPAR-γ)[83,84]. M2 macrophages that are stimulated by CB_2 receptor agonists display increased phagocytic ability and diminished antigen presentation, both of which are vital for resolving inflammation and conducting tissue repair[85,86]. In dendritic cells (DCs), activation of CB_2 decreases the expression of MHC-II and co-stimulatory molecules (CD80, CD86), hinders maturation, and reduces their capacity to activate naïve T cells[87]. These consequences produce a tolerogenic DC phenotype that lessens T-cell activation and promotes immune resolution[88,89]. The ability of CB_2 receptors to inhibit the migration of dendritic cells to lymph nodes through the downregulation of CCR7 and changes in cytoskeletal structures further limits immune amplification[90,91]. T lymphocytes exhibit low baseline expression of the CB_2 receptor, but this expression increases significantly upon activation[8], [92–95]. CB_2 receptor signaling in CD4+ T cells restricts proliferation and differentiation into Th1 and Th17 subsets while encouraging the development of regulatory T cells (Tregs)[89,93,96–99,100–105]. This immunosuppressive action is partially facilitated by reducing the secretion of IL-2, IFN-γ, and IL-17, as well as modulating transcription factors like T-bet and RORγt. T cells that lack CB_2 receptor exhibit heightened inflammatory responses in colitis and encephalomyelitis models, reinforcing its role in immune regulation[97,99–102,103–108,109–114]. B cells express high levels of the CB_2 receptor, and its activation influences antibody production, class switching, and migration[115,116]. CB_2 receptor influences germinal center dynamics and the formation of B cell memory, although the underlying mechanisms continue to be explored. CB_2 receptor supports tissue retention and chemotaxis in marginal zone B cells through gradients dependent on 2-AG[117–119].

CB_2 receptor also interacts with the wider eCBome through connections with prostaglandins, lysophospholipids, and nuclear receptors like PPARs[120–123]. For example, IL-10 production induced by CB_2 receptor works synergistically with PPARγ activation in macrophages to promote the resolution of inflammation[124–126]. Interactions with TRP channels and adenosine receptors also regulate leukocyte activity and migration[127,128].

In conclusion, CB_2 receptor orchestrates a complex immunoregulatory program that balances host defense and immune tolerance. Its ability to modulate cytokine networks, antigen presentation, leukocyte trafficking, and adaptive cell differentiation highlights its potential as a therapeutic target in chronic inflammation, autoimmunity, and tissue damage. Precisely targeting CB_2 receptor with full agonists, PAMs, or biased ligands presents a novel strategy for adjusting immune function without broadly suppressing host immunity.

5. CB_2 Receptor and Microglia in Neuroinflammation

Microglia, the brain's resident macrophages, are crucial for preserving CNS homeostasis and managing immune responses during injury and disease[129]. In a healthy brain, microglia exhibit a surveying state characterized by branching shapes and minimal expression of inflammatory proteins[130]. When faced with pathological triggers such as infection, trauma, or neurodegeneration, microglia quickly transform morphologically and functionally into reactive states, which are generally classified as M1 (pro-inflammatory) or M2 (anti-

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inflammatory/neuroprotective[131,132]. Although this M1/M2 classification is somewhat simplistic, it serves as a helpful conceptual framework for understanding immune polarization in the CNS. Notably, the CB_2 receptor appears to play a vital role in regulating this polarization. Under normal circumstances, CB_2 receptor expression in microglia is low or undetectable; however, it is rapidly increased in response to immune activation, oxidative stress, and neuroinflammatory stimuli[133]. This ability to be induced makes CB_2 receptor a context-dependent immunomodulator that can finely adjust the equilibrium between neurotoxic and neuroprotective states[134]. Activation of CB_2 receptor has been demonstrated to decrease the release of pro-inflammatory cytokines while enhancing anti-inflammatory mediators[135]. Mechanistically, activating the CB_2 receptor prevents the nuclear translocation of NF-κB, diminishes MAPK pathway activation, and modulates the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), thereby dampening the pro-inflammatory signaling cascade at several levels[136–138].

Recent studies conducted both in vivo and in vitro support the role of the CB_2 receptor in modulating the microglial phenotype. For instance, activation of the CB_2 receptor promotes a transition from M1 to M2 phenotypes, as evidenced by decreased expression of inducible nitric oxide synthase (iNOS) and increased levels of arginase-1 (Arg-1)[139,140]. In models of Alzheimer's disease, traumatic brain injuries, and stroke, pharmacological stimulation of CB_2 receptors has lessened neuroinflammation, reduced neuronal death, improved cognitive functioning, and minimized gliosis[141]. In conditions like neuropathic pain and multiple sclerosis, CB_2 receptor signaling has been found to reduce neurotoxicity caused by microglia and promote remyelination[142]. Epigenetic mechanisms also play a role in regulating the CB_2 receptor in microglia. Modifications to histones, such as increased H3K4me3 and decreased H3K27me3 at the *CNR2* promoter, have been associated with the transcriptional activation of CB_2 receptor during inflammatory responses[143,144].

Furthermore, the expression of CB_2 receptor can be influenced by non-coding RNAs (like miR-139), which inhibit *CNR2* translation under normal conditions but are downregulated during inflammation[145]. These regulatory processes highlight the dynamic adaptability of CB_2 receptor expression and its potential as a therapeutic target in neuroimmune disorders. Significantly, the activation of CB_2 receptors affects synaptic plasticity by modulating microglial behavior[146,147]. Activated microglia can affect neuronal circuits by pruning synapses and releasing neurotrophic factors. By influencing microglial activity, CB_2 receptor indirectly affects the stability and repair of neural networks. This aspect of neuromodulation has significant implications for disorders such as schizophrenia and depression, where abnormal synaptic pruning and ongoing neuroinflammation play a role[148]. In summary, the signaling of CB_2 receptors in microglia represents a significant intersection between immune modulation and neural repair. Targeting CB_2 receptor presents a comprehensive approach for reducing neuroinflammation, restoring immune balance, and safeguarding neural integrity, making it a foundational element in cannabinoid-based therapies for CNS disorders.

6. CB_2 Receptor in Depression and Psychiatric Disorders

Depression is increasingly acknowledged as a complex disorder involving the neuroimmune system, marked by a subtle interaction between chronic inflammation, improper stress response regulation, reduced neuroplasticity, and altered microglial cell activity[149]. This condition is not simply due to a lack of neurotransmitters; instead, its underlying pathophysiology consists of intricate relationships between the immune system and the CNS, shaped by both psychosocial influences and biological stress factors[150]. Significant factors contributing to this disorder include immune cell activation, increased levels of pro-inflammatory cytokines, and overactivity of the hypothalamic-pituitary-adrenal (HPA) axis[151,152]. These components result in synaptic malfunction, amplified glial reactivity, and long-lasting changes in neural circuits, creating a challenging environment for those affected by depression[153,154].

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Within this complex framework, the cannabinoid receptor CB_2 has emerged as a crucial component in regulating the interaction between the immune system and neurological processes. Traditionally associated with immune responses in the periphery, recent studies have revealed the presence of CB_2 receptors in the brain, particularly in response to stress and inflammation[152,155–157]. The increased expression of the CB_2 receptor in glial cells and areas of the brain that respond to stress is now increasingly considered a compensatory strategy aimed at restoring equilibrium[145]. Through its signaling pathways, CB_2 can reduce neurotoxicity caused by cytokines, influence the release of glucocorticoids, and promote neurotrophic signaling[158]. This positions CB_2 as a central player in mechanisms that regulate mood and are influenced by the immune system. This section examines the various roles of CB_2 receptors in neuroimmune regulation during depressive episodes, with a focus on the dynamics of cytokines, modulation of the HPA axis, epigenetic changes, and behavioral traits observed in preclinical studies. The knowledge gained from these studies provides a strong justification for investigating the therapeutic potential of targeting CB_2 receptors in treating inflammation-related mood disorders, while avoiding the psychotropic side effects typically associated with CB_1 receptor activation.

6.1. Neuroimmune Pathology and CB_2 Receptor Expression

Numerous studies indicate a strong correlation between depressive symptoms and states of neuroinflammation. Elevated concentrations of pro-inflammatory cytokines, such as TNF-α, IL-1β, and IL-6, are frequently found in the serum and cerebrospinal fluid of individuals with depression[159,160]. These cytokines interfere with neurotransmission by decreasing serotonin production (through the IDO-mediated metabolism of tryptophan), hindering neurogenesis in the hippocampus, and enhancing excitotoxicity. Furthermore, chronic stress triggers the activation of microglia and immune cells, leading to a systemic inflammatory response that worsens neurobiological impairments[161]. Research has shown increased levels of CB_2 receptor expression in brain tissues and immune cells of animal models and humans with major depressive disorder (MDD). This upregulation of CB_2 receptor appears to respond to inflammatory stimuli and stress hormones, functioning as a potential compensatory mechanism to restore balance[162,163]. Collectively, these findings suggest that the increase of CB_2 receptors in depressive states may reflect an adaptive neuroimmune strategy intended to counteract neuronal and behavioral deficits caused by inflammation.

6.2. Modulation of the HPA Axis and Inflammatory Feedback

The HPA axis regulates stress responses through the secretion of glucocorticoids. Chronic stress leads to persistent activation of this axis, which hampers the regulation of cortisol by the hippocampus and contributes to depressive disorders. Activation of CB_2 receptor has been found to alleviate excessive HPA activity, likely by reducing both central and peripheral inflammation. CB_2 receptor signaling diminishes the production of pro-inflammatory cytokines that typically contribute to HPA hyperactivity[164]. Notably, CB_2 receptors may play a dual regulatory function by modulating cytokine release from immune cells and by inhibiting neuronal hyperexcitability in stress-sensitive areas such as the hippocampus and prefrontal cortex[165,166]. Pharmacological stimulation of CB_2 receptors has been shown to normalize serum corticosterone levels, diminish glial reactivity, and restore expression of brain-derived neurotrophic factor (BDNF), all of which are crucial for mood regulation and synaptic plasticity[156,167,168].

6.3. Epigenetic Regulation and Transcriptional Modulation

Epigenetic processes closely regulate CB_2 receptor expression in the context of depression. Modifications to histones, such as increased levels of H3K4me3 and H3K9ac and diminished repressive marks (H3K9me2, H3K27me3) at the *CNR2* promoter, promote CB_2 receptor transcription in response to stress and inflammation[52]. Additionally, the methylation status of the CpG islands

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located upstream of *CNR2* can either repress or activate transcription, depending on exposure to environmental stressors[169]. Transcription factors such as nuclear erythroid 2-related factor 2 (NRF-2), NF-κB, and Activator Protein-1 (AP-1) have been associated with the regulation of the CB_2 receptor gene[170]. NRF-2 connects oxidative stress responses with the activation of the CB_2 receptor[171]. When exposed to stress, the translocation of these transcription factors to the nucleus can trigger the transcription of *CNR2,* suggesting a dynamic interaction among redox status, inflammation, and cannabinoid signaling[52]. MeCP2 plays a key role in maintaining the *CNR2* gene in a transcriptionally repressed state under homeostatic conditions by binding to methylated CpG islands within its promoter region[172]. This repression is alleviated during stress or inflammatory responses through phosphorylation of MeCP2, which reduces its DNA-binding affinity and facilitates gene activation. The demethylation of the *CNR2* promoter is mediated through two primary mechanisms: the deaminase pathway involving AID/APOBEC enzymes and the TET protein pathway, both of which initiate DNA base modifications that are resolved through the base excision repair (BER) system. These events ultimately replace methylated cytosines with unmethylated ones, enabling transcription of *CNR2* and increased CB_2 receptor expression in microglia. This epigenetic switch illustrates how MeCP2 functions as a dynamic regulator of CB_2 receptor expression in response to environmental and inflammatory stimuli [172,173].

6.4. Behavioral Evidence from Animal Models

Research on rodents using CB_2 receptor agonists like JWH133 and β-caryophyllene has shown significant antidepressant-like effects in models of chronic stress and lipopolysaccharide (LPS)-induced depression[77,96,168]. These effects include reduced immobility in forced swim tests, enhanced sucrose preference, normalized HPA axis functioning, and restoration of neurogenesis in the hippocampus. In contrast, CB_2 receptor knockout mice display increased anxiety, social withdrawal, and heightened inflammatory responses that reflect critical features of depressive disorders. Notably, activation of CB_2 receptor reduces microglial activation and inhibits TLR4-mediated signaling, which is integral to the inflammatory mechanisms underlying depression. Moreover, microglia deficient in CB_2 receptor show increased production of nitric oxide and inflammatory cytokines, further underscoring the immunosuppressive role of this receptor[146].

6.5. Therapeutic Implications and Drug Development

Selective CB_2 receptor agonists are a new category of potential antidepressants that possess anti-inflammatory and neuroprotective characteristics without causing psychoactive effects associated with CB_1 receptor. Compounds such as HU-910, AM1241, and BCP exhibit anxiolytic and antidepressant effects in various preclinical studies[96,174]. Additionally, PAMs of CB_2 receptor could increase endocannabinoid levels without directly stimulating the receptor, providing more refined control with reduced side effects. Notably, therapies targeting CB_2 receptors could work in conjunction with selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) by modulating the inflammatory environment, thereby diminishing the effectiveness of monoamines[149]. For instance, activating CB_2 receptors may restore glucocorticoid receptor sensitivity, boost BDNF levels, and enhance neuroplasticity, thus addressing the complex nature of depression. Overall, CB_2 receptors have a significant role in both immune regulation and neuroprotection in the context of depression. CB_2 receptor acts as a link between the immune system and CNS functions by modulating inflammation, releasing stress hormones, synaptic adaptability, and glial responsiveness. Future studies should focus on developing CB_2 receptor-selective compounds, examining their combined use with current antidepressants, and further investigating their epigenetic influences to maximize therapeutic outcomes.

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7. CB_2 Receptor in Chronic Pain and Neuropathy

Chronic pain is a complex condition affecting millions around the world, often resulting from prolonged tissue damage, nerve injury, or disrupted neuroimmune signaling. It includes various types, such as inflammatory pain, pain related to cancer, and neuropathic pain[175–178]. Neuropathic pain occurs due to injuries or dysfunctions in the somatosensory system and often proves resistant to traditional pain relievers like nonsteroidal anti-inflammatory drugs (NSAIDs) or opioids[179–181]. There is growing evidence that the endocannabinoid system, particularly the CB_2 receptor, plays a significant role in managing chronic and neuropathic pain through immune regulation, glial signaling, and peripheral neuronal pathways.

7.1. Immune and Glial Contributions to Chronic Pain

Ongoing nociception is closely associated with the activation of the immune system. After a nerve injury, peripheral immune cells (such as macrophages and neutrophils) move into the site of injury, releasing pro-inflammatory substances like IL-6, TNF-α, and prostaglandins. These mediators make nociceptors more sensitive by altering ion channels and increasing receptor expression at the peripheral ends[182,183]. At the same time, microglia and astrocytes in the spinal cord and dorsal root ganglia (DRG) become active, furthering neuroinflammation by secreting cytokines, chemokines, and ROS. This interaction between glial and neuronal cells maintains central sensitization and allodynia. Significantly, following peripheral nerve injury, CB_2 receptor expression rises in DRG macrophages, spinal microglia, and astrocytes. This increase makes the CB_2 receptor a crucial molecular regulator that can help control excessive neuroimmune activation[184].

7.2. CB_2 Receptor Activation in Pain Modulation

CB_2 receptor agonists have demonstrated strong pain-relieving effects in various models of inflammatory and neuropathic pain[182]. In contrast to CB_1 receptor agonists, which might cause side effects in the CNS, such as sedation and dysphoria, CB_2 receptor-selective compounds provide pain relief without psychoactive effects due to their limited ability to penetrate the CNS or their preferential expression in activated immune cells[156]. Studies conducted in preclinical settings using CB_2 receptor agonists, such as JWH-133, AM1241, BCP, and HU-910, have exhibited significant reductions in mechanical and thermal hyperalgesia[140]. These outcomes are attributed to diminished glial activation, a reduction in pro-inflammatory cytokines, and the prevention of nociceptor sensitization. Activation of the CB_2 receptor leads to the downregulation of the NF-κB and MAPK signaling pathways, which in turn lowers iNOS, cyclooxygenase-2 (COX-2), and chemokine levels at the injury site. In both spinal cord slices and in vivo models, the administration of CB_2 receptor agonists has been shown to decrease excitatory neurotransmission by inhibiting glutamate release and restricting synaptic facilitation at dorsal horn neurons. Concurrently, CB_2 receptor activation boosts inhibitory GABAergic and glycinergic signaling, thereby restoring the excitatory-inhibitory balance disrupted in chronic pain conditions[163].

7.3. Endocannabinoid Tone and Peripheral Mechanisms

The two main endocannabinoids, 2-AG and AEA, are generated on demand by neurons and immune cells in reaction to injury. These substances activate CB_2 receptors in peripheral immune cells and spinal microglia, thereby modulating nociceptive signaling locally. The regulation of endocannabinoid tone through enzymes such as DAGL, MAGL, and FAAH is crucial for managing CB_2 receptor-mediated analgesia. Notably, inhibiting MAGL not only increases the levels of 2-AG but also reduces the production of prostaglandins, thereby further aiding in pain relief. Strategies that combine CB_2 receptor agonists with FAAH inhibitors have shown enhanced analgesic effects, highlighting the significance of endogenous ligand support for the control mediated by CB_2 receptor[4,139].

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7.4. Cannabinoid Synergy and CB_1 Receptor/ CB_2 Receptor-Independent Pathways

Phytocannabinoids, such as cannabidiol (CBD) and cannabigerol (CBG), exhibit anti-inflammatory and pain-relieving effects, which are often partially mediated through CB_2 receptor signaling[4]. CBG functions as a weak antagonist of CB_1 receptor and a partial agonist of CB_2 receptor while also interacting with TRP channels and α2-adrenergic receptors[185]. In models of neuropathic pain, CBG alleviates hypersensitivity and mitigates the effects of microglial activation, which are reversed by CB_2 receptor antagonists, indicating its dependence on CB_2 receptors[186]. Importantly, the combination of CBD and CBG exhibits synergistic effects, likely resulting from their joint action on CB_2 receptors and TRP channels, as well as the suppression of cytokine release. This interaction between multiple receptors enhances the overall inhibition of neuroinflammatory pain pathways. Clinical investigations of balanced THC: CBD formulations such as nabiximols (Sativex®) have demonstrated effectiveness in treating neuropathic pain associated with multiple sclerosis, although the roles of CB_2 receptor compared to CB_1 receptor continue to be explored[187].

7.5. Immunological Insights and Translational Promise

From an immunological perspective, activating CB_2 receptors reduces the infiltration of peripheral macrophages, shifts macrophage phenotype from M1 to M2, and decreases spinal microglial activation, all of which are essential for resolving neuroinflammation[172]. In mice lacking the CB_2 receptor, observations have been made of heightened mechanical allodynia, prolonged cytokine levels, and increased glial reactivity following nerve injury, confirming the receptor's role in regulating pain through immune mechanisms[188]. Notably, CB_2 receptor signaling also influences mast cell degranulation and the movement of neutrophils in states of inflammatory pain, thereby broadening its relevance to visceral pain and autoimmune-related syndromes. In research models for rheumatoid arthritis and colitis, agonizing CB_2 receptor diminishes the trafficking of leukocytes and lessens nociceptive hypersensitivity, indicating the receptor's involvement in the broader immune-pain interaction[163]. There is a scarcity of clinical trials targeting the CB_2 receptor for pain management; however, selective ligands are beginning to undergo early-phase assessments. The limited expression of CB_2 receptor in disease-activated cells and the absence of CNS side effects underscore its potential as an appealing target for next-generation analgesics.

8. CB_2 Receptor in Schizophrenia and Dopaminergic Circuits

Schizophrenia is a multifaceted neuropsychiatric condition marked by positive symptoms (like hallucinations and delusions), negative symptoms (such as anhedonia and social withdrawal), and cognitive impairments. While earlier theories focused on dopaminergic dysregulation, particularly the heightened activity within the mesolimbic pathway, recent developments have broadened the etiological understanding to incorporate glutamatergic imbalance, neurodevelopmental irregularities, oxidative stress, and neuroinflammation[66,148]. Significantly, new evidence suggests that the endocannabinoid system, particularly the signaling of CB_2 receptors, plays a role in modulating various interconnected pathological areas.

8.1. CB_2 Receptor Expression in Schizophrenia-Relevant Brain Circuits

Historically, CB_2 receptor was viewed mainly as a peripheral receptor; however, it is now recognized to be inducibly expressed in numerous CNS regions relevant to schizophrenia, including the ventral tegmental area (VTA), nucleus accumbens (NAc), prefrontal cortex (PFC), and hippocampus. CB_2 receptor mRNA and protein have been identified in dopamine neurons, cortical pyramidal neurons, and glial cells under pathological circumstances through RNAscope, immunohistochemistry, and single-cell transcriptomics[66,189]. In the context of inflammation, excitotoxic stress, and dopaminergic overactivity, key features of the schizophrenic brain, CB_2 receptor expression is notably upregulated. Studies in rodents have demonstrated that CB_2 receptor is present in both the VTA's tyrosine hydroxylase-positive (dopaminergic) neurons and medium

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spiny neurons (MSNs) expressing D1 or D2 in the NAc[190]. The activation of CB_2 receptor in these areas leads to decreased neuronal excitability and reduced dopamine release, indicating a role in regulating dopaminergic tone.

8.2. CB_2 Receptor Modulation of Dopamine Signaling

The agonism of the CB_2 receptor results in neuronal hyperpolarization within dopaminergic circuits, which diminishes after depolarization and decreases dopamine release in key regions such as the striatum and PFC. Preclinical research utilizing selective CB_2 receptor agonists (JWH-133) has demonstrated that the activation of CB_2 receptors inhibits the hyperactivity of VTA dopamine neurons both in vitro and in vivo. Micro-dialysis investigations indicate that the administration of CB_2 receptor agonists into the NAc significantly decreases extracellular dopamine levels, while CB_2 receptor antagonists (AM630) enhance dopaminergic activity[140,190]. These effects do not occur in CB_2 receptor knockout mice, confirming the receptor specificity of the impact. This bidirectional modulation implies that CB_2 receptor signaling establishes a negative feedback mechanism within mesolimbic circuits. As hyperdopaminergic activity in the striatum is linked to psychotic symptoms, the attenuation by CB_2 receptor may serve to balance dopaminergic overactivity, presenting a potential mechanism for antipsychotic-like effects without the motor side effects associated with D2 antagonists.

8.3. Genetic and Epigenetic Links to Schizophrenia

Genetic research has further indicated the role of the CB_2 receptor in schizophrenia. Variations in the *CNR2* gene, specifically single-nucleotide polymorphisms (SNPs), have been linked to an increased risk of psychosis, decreased CB_2 receptor expression, and altered inflammatory gene networks. For example, the Q63R polymorphism has been associated with reduced functionality of the CB_2 receptor and increased susceptibility to stress-related behavioral traits. In patients with schizophrenia, notable changes in methylation patterns and histone modifications are observed at the *CNR2* gene locus due to epigenetic factors[191]. Environmental stressors, infections, and toxins recognized as risk factors for schizophrenia can trigger epigenetic alterations in CB_2 receptor expression within the CNS. These observations highlight the CB_2 receptor as a critical point of interaction between genes and environmental influences in this disorder.

8.4. CB_2 Receptor in Neuroinflammation and Glial Dysfunction

Neuroinflammation plays a significant role in the development of schizophrenia. Consistently, elevated levels of IL-6, TNF-α, and activated microglia have been observed in both postmortem studies and in vivo imaging of individuals with schizophrenia[192]. CB_2 receptors are potent regulators of immune responses, playing a crucial role in modulating the phenotype of microglia and the release of cytokines. In cases where the CB_2 receptor is absent, studies in mice have shown worsened inflammatory reactions and behavioral abnormalities similar to those seen in schizophrenia, such as reduced prepulse inhibition (PPI), altered social behavior, and heightened locomotor activity in response to psychostimulants. On the other hand, activating CB_2 receptor pharmacologically has been shown to reverse PPI deficits caused by MK-801 and restore abnormal dopamine signaling in models of schizophrenia[148]. Furthermore, the CB_2 receptor influences synaptic pruning by microglia, a process that is increasingly recognized as relevant to schizophrenia. Overactive pruning during the adolescent period may contribute to the cortical thinning and synapse loss observed in affected individuals. The activation of CB_2 receptor helps limit excessive microglial activity and may contribute to restoring synaptic balance, influencing neurodevelopmental pathways.

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8.5. Endocannabinoid Tone and CB_2 Receptor Signaling Bias

The endocannabinoids 2-AG and AEA impact CB_2 receptor activity within the brain. In models of schizophrenia, levels of 2-AG are frequently found to be increased, and the dysregulation of enzymes that break down endocannabinoids, such as MAGL and FAAH, leads to circuit imbalances[193]. Importantly, the activation of CB_2 receptor can direct signaling toward either anti-inflammatory or neuroprotective pathways depending on the specific ligand and the cellular environment. Using biased CB_2 receptor ligands or PAMs could enhance the precision of therapeutic interventions. For instance, EC21a, a particular compound, selectively promotes CB_2 receptor-mediated anti-inflammatory and antinociceptive effects without fully activating the receptor, thereby minimizing potential side effects.

8.6. Translational Implications

Unlike conventional antipsychotic medications that primarily target dopamine D2 receptors and often lead to extrapyramidal symptoms, the modulation of CB_2 receptors presents a distinct mechanism of action with better safety profiles. CB_2 receptor agonists have the potential to address both hyperdopaminergic and neuroinflammatory conditions, thereby impacting various symptoms associated with schizophrenia. Although clinical trials focusing on the CB_2 receptor are currently limited, their number is increasing. Considering the multifaceted causes of schizophrenia, approaches that target multiple pathways, such as the combination of CB_2 receptor agonism with glutamatergic or neurotrophic strategies, could prove to be effective. The convergence of cannabinoid signaling, immune system regulation, and synaptic plasticity positions the CB_2 receptor as a promising target in the field of psychopharmacology.

9. CB_2 Receptor in Autoimmune and Inflammatory Diseases

Autoimmune and inflammatory disorders are intricate conditions characterized by dysfunctional immune responses, tissue damage, and prolonged inflammation, often instigated by a loss of immunological tolerance. Through the modulation of CB_2 receptors, the ECS has surfaced as an essential regulator in managing heightened immune responses and re-establishing tissue balance. It has demonstrated protective properties in various models of autoimmune diseases.

9.1. CB_2 Receptors in Asthma and Related Diseases: Immune Regulation, Innate Cell Crosstalk, and Therapeutic Paradox

Asthma is a long-lasting inflammatory condition of the airways characterized by fluctuating airflow obstruction, infiltration by eosinophils, excessive mucus production, and a prominent type 2 cytokine environment, often influenced by both innate and adaptive immune systems[194,195]. Growing research suggests that the CB_2 receptors act as a modulator of immune cell activation and tissue inflammation within this framework[114,196,197]. However, contrary to its anti-inflammatory role in various autoimmune contexts, CB_2R seems to exhibit a dual, and at times pro-inflammatory, function in allergic airway disease[73,114,197,198].

Ferrini et al. (2017) presented persuasive evidence that activating CB_2R fosters allergic airway inflammation in mice exposed to house dust mites (HDM). In their study, mice lacking CB_2 ($CB_2^{-/-}$) displayed significantly lower levels of airway inflammation, with less eosinophilic infiltration, reduced recruitment of $CD4^+$ T cells, and decreased mucus production, compared to wild-type (WT) controls[197]. Notably, this decline was not attributed to any shortcomings in adaptive immunity but instead connected to changes within the innate immune landscape of the lungs. $CB_2^{-/-}$ mice exhibited a significant increase in the number of pulmonary NK cells, particularly those expressing DX5, NKp46, and granzyme A, which produced high levels of IFN-γ without generating Th2 cytokines. These NK cells negatively regulated group 2 innate lymphoid cells (ILC2s), which are critical producers of IL-5 and IL-13 during allergic reactions. The rise in IFN-γ-producing NK cells correlated

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with a suppression of ILC2 numbers and their function, implying a new immunoregulatory circuit through which CB_2R influences asthma development via the NK–ILC2 axis[197,199].

The causal significance of this pathway was further confirmed through both depletion and adoptive transfer experiments. Depleting NK cells in $CB_2^{-}/^{-}$ mice restored allergic airway inflammation and increased the presence of IL-13-expressing ILC2s, while transferring $CB_2^{-}/^{-}$ NK cells into WT mice inhibited HDM-induced inflammation. This evidence indicates that CB_2R signaling limits NK cell accumulation and IFN-γ production, thereby allowing for increased ILC2-driven type 2 responses. Mechanistically, endocannabinoids such as 2-AG inhibited IFN-γ secretion from activated NK cells in vitro, suggesting that CB_2 receptors act as a negative regulator of NK cell activity in the lungs[197,200]. Pharmacological investigations further supported this notion. Administering a CB_2 antagonist intranasally in WT mice replicated the phenotype observed in $CB_2^{-}/^{-}$ mice, reducing HDM-induced eosinophilia, $CD4^{+}$ T cell influx, and goblet cell hyperplasia. Conversely, the CB_2-selective agonist HU-308 intensified allergic inflammation, aligning with the receptor's pro-inflammatory impact in this scenario[197]. Additional research by Frei et al. (2016) also demonstrated that CB_2 receptor activation enhances eosinophil migration and responsiveness in allergen challenge models, suggesting that CB_2 receptor signaling may exacerbate eosinophil-dependent inflammation during asthma flare-up[198]. Moreover, Mimura et al. (2012) noted the role of endocannabinoids, such as 2-AG, in allergic inflammation, showing that endogenous ligands acting on the CB_2 receptor can affect immune cell migration and chemokine expression, including CCL2, a key player in Th2 polarization[201,202]. As such, 2-AG can be biosynthesized by eosinophils and is a potent inducer of their migration[203–206]. Ferrini et al. (2017) found that $CB_2^{-}/^{-}$ mice exhibited a significant reduction in CCL2 production and levels of type 2 cytokines (IL-4, IL-5, and IL-13) after allergen exposure[197].

In summary, these findings place CB_2R at a crucial crossroads between the regulation of innate immunity and allergic inflammation. Unlike its suppressive effects observed in autoimmunity, CB_2R signaling in asthma seems to restrain NK cells that would typically inhibit ILC2-driven eosinophilic responses. This paradox highlights the need for targeted strategies that are specifically tailored to the disease and cell type. Future treatment methods could benefit from selectively influencing CB_2 receptor signaling within specific immune subsets or utilizing biased agonism to refine their immune-regulatory effects in allergic conditions.

9.2. CB_2 Receptor in Multiple Sclerosis (MS)

Autoreactive CD4+ T cells invade the CNS and promote demyelination, neurodegeneration, and functional deficits in multiple sclerosis[207]. CB_2 receptor expression is elevated in activated microglia and immune cells penetrating the spinal cord during experimental autoimmune encephalomyelitis (EAE), a mouse model for MS[208]. The use of CB_2 receptor agonists like JWH-133 or BCP reduces the severity of the disease, diminishes CNS immune cell infiltration, and lowers levels of pro-inflammatory cytokines such as IL-17A, IFN-γ, and TNF-α[96,209]. Mechanistically, activating CB_2 receptor hinders NF-κB translocation and the formation of the NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome, thus limiting the inflammatory response. Mice lacking CB_2 receptors exhibit aggravated EAE outcomes and more pronounced myelin damage, indicating that the endogenously increased CB_2 receptor offers a necessary regulatory mechanism against autoimmunity.

9.3. CB_2 Receptor in Rheumatoid Arthritis

Rheumatoid arthritis (RA) is characterized by the infiltration of macrophages, T cells, and fibroblast-like synoviocytes (FLS) into the joints, resulting in cartilage degradation and bone damage. CB_2 receptor is predominantly expressed in synovial macrophages and FLS. The stimulation of CB_2 receptor leads to the inhibition of matrix metalloproteinase-3 (MMP-3) and MMP-9 secretion, decreases TNF-α and IL-6 levels, and diminishes oxidative stress by lowering iNOS and nitric oxide (NO) levels[210]. In models of collagen-induced arthritis, CB_2 receptor agonists reduce paw swelling

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and joint tissue damage[211]. Variants in the *CNR2* gene, such as Q63R, have been associated with a higher risk of developing RA and more severe forms of the disease, underscoring the significance of the CB_2 receptor in the pathogenesis of RA[212]. Additionally, the CB_2 receptor facilitates M2 macrophage polarization and boosts regulatory T-cell (Treg) responses, which contribute to its immune-resolution capabilities.

9.4. CB_2 Receptor in Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is characterized by hyperactive B cells, irregular dendritic cell signaling, and excessive production of type I interferons. The presence of CB_2 receptors in B cells can mitigate B-cell receptor-mediated growth and antibody generation. CB_2 receptor agonists have been shown to reduce the levels of anti-dsDNA autoantibodies and lessen the severity of glomerulonephritis in lupus-prone mice[213,214]. Notably, CB_2 receptor curtails TLR7/9-mediated IFN-α production from plasmacytoid dendritic cells (pDCs), which is a key pathway for cytokine activity in lupus[215]. It also promotes myeloid-derived suppressor cells (MDSCs) that secrete IL-10, aiding in immune regulation and reducing autoreactive responses. Changes in *CNR2* expression and signaling among SLE patients highlight its potential as both a biomarker for the disease and a therapeutic target.

9.5. CB_2 Receptor in Inflammatory Bowel Disease

Inflammatory Bowel Disease (IBD), which includes Crohn's disease and ulcerative colitis, is characterized by chronic recurring inflammation of the gastrointestinal (GI) tract, resulting from an immune response to gut microbiota that is improperly regulated in individuals with a genetic susceptibility[216]. In IBD, the mucosal immune system becomes pathologically overactive, characterized by an exaggerated release of cytokines, dysfunction of the epithelial barrier, and persistent infiltration of immune cells, including T cells, neutrophils, and macrophages. Recently, CB_2 receptor has been recognized as a critical immunoregulatory modulator in the intestinal microenvironment.

CB_2 receptor is present at low levels in a healthy gut but shows a significant increase during periods of acute inflammation, particularly in lamina propria macrophages, CD4+ T cells, dendritic cells, and intestinal epithelial cells. In human biopsies from patients with IBD and preclinical mouse models, particularly those with dextran sulfate sodium (DSS)- and trinitrobenzene sulfonic acid (TNBS)-induced colitis, the expression of CB_2 receptor is linked to disease severity and immune cell activation[217]. Immunohistochemical studies highlight the presence of CB_2 receptor in the inflamed colonic mucosa, while flow cytometry confirms its elevated levels in infiltrating leukocytes. When activated by selective agonists such as JWH-133, HU-308, or AM1241, CB_2 receptor signaling has several protective effects within the gut. These effects include reducing the expression of pro-inflammatory cytokines (for example, TNF-α, IL-1β, IL-6, and IL-12), inhibiting neutrophil chemotaxis and oxidative bursts, and decreasing the expression of endothelial cell adhesion molecules, which helps to limit the migration of leukocytes into inflamed tissues. Additionally, CB_2 receptor activation enhances levels of anti-inflammatory mediators such as IL-10 and promotes tolerogenic dendritic cell phenotypes, leading to a more balanced mucosal immune response.

Importantly, CB_2 receptor also supports the integrity of the intestinal epithelial barrier, a key aspect of IBD pathology. Activation of CB_2 receptor restores tight junction proteins like occludin, claudin-1, and ZO-1, which are often downregulated in IBD, resulting in increased intestinal permeability, commonly referred to as leaky gut. Furthermore, CB_2 receptor stimulation reduces epithelial apoptosis and promotes wound healing, as demonstrated by organoid and epithelial scratch assays[140,218,219]. These benefits to the epithelium occur partly through interaction with the PI3K/Akt pathway, which is critical for cell survival and growth. CB_2 receptor signaling is also closely associated with other immuno-metabolic pathways in the gut, particularly PPAR-γ and TRPV1. The activation of CB_2 receptor enhances the nuclear translocation of PPAR-γ in macrophages and epithelial cells, bolstering anti-inflammatory transcriptional programs[220,221]. At the same

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time, CB_2 receptor reduces TRPV1-mediated neurogenic inflammation by modulating the signaling of capsaicin-sensitive afferent nerves and the output of cytokines[222–224]. This interconnected functional axis (CB_2 receptor–PPAR-γ–TRPV1) thus serves as a significant regulatory hub in intestinal inflammation.

Research using knockout models further emphasizes the contribution of CB_2 receptors to IBD pathogenesis. Mice lacking CB_2 receptor (*Cnr2*−/−) that were subjected to DSS or TNBS show more severe colitis, as evident by greater body weight loss, shortened colon lengths, increased histopathological scores, and elevated levels of inflammatory cytokines and ROS[225–227]. In contrast, pharmacological activation of CB_2 receptor alleviates these pathological features and reduces fibrosis, a common complication associated with chronic IBD, by inhibiting TGF-β signaling and preventing fibroblast activation. From a translational viewpoint, therapies targeting CB_2 receptor present promising adjunctive options for IBD management. CB_2 receptor activation has been associated with the upregulation of PPAR-γ signaling pathways, potentially contributing to anti-inflammatory responses in immune and epithelial cells through indirect crosstalk mechanisms[228]. Furthermore, because CB_2 receptor activation does not produce psychoactive effects, it represents a safer alternative compared to interventions targeting CB_1 receptor. Nonetheless, challenges persist in developing CB_2 receptor agonists that are specifically targeted to the gut and are peripherally restricted to minimize off-target effects while ensuring receptor selectivity. In conclusion, signaling through the CB_2 receptor plays a complex role in the development and resolution of IBD. It influences both immune cell functions and components of the intestinal epithelium to facilitate anti-inflammatory, barrier-protective, and antifibrotic responses. As a context-sensitive and inducible immunomodulator, CB_2 receptor represents a promising target for therapeutic strategies aimed at modifying chronic gut inflammation, restoring mucosal balance, and enhancing outcomes for patients with IBD.

9.6. Therapeutic Perspectives

Focusing on the CB_2 receptor provides an intriguing approach for treating autoimmune and chronic inflammatory conditions, as it can alter immune responses without causing psychoactive effects. The expression of CB_2 receptor can be induced in immune cells and inflamed tissues, making it a responsive and disease-related therapeutic target. In preclinical studies involving conditions such as MS, RA, IBD, and SLE, activation of the CB_2 receptor reduces the release of inflammatory cytokines, limits the recruitment of leukocytes, and aids in tissue repair.

10. CB_2 Receptor in Cancer and Immune Checkpoint Modulation

CB_2 receptor has been recognized as an unconventional but highly promising target for immunomodulation in cancer biology. Its presence in the tumor microenvironment (TME) and its role in immune regulation establish the CB_2 receptor as a modulator of tumor progression and a possible complement to immune checkpoint therapy[229]. This section examines the functions of the CB_2 receptor within the TME, its connection with immune checkpoint molecules, and its potential applications in clinical settings.

10.1. CB_2 Receptor Expression in the Tumor Microenvironment and Immune Checkpoints

CB_2 receptor is found at elevated levels in various tumors, including hematologic malignancies and solid tumors like breast, lung, colorectal, pancreatic, and glioblastoma[230–232]. Within the TME, CB_2 receptor is particularly concentrated in immunosuppressive niches, including tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), regulatory T cells (Tregs), and exhausted CD8+ T cells[233,234–237]. CB_2 receptor influences leukocyte infiltration, angiogenesis, and the metabolic reprogramming of immune cells. In models of melanoma and glioma, activating CB_2 receptors has been shown to reduce pro-tumorigenic inflammation while restoring effector immune activities[238].

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Emerging evidence suggests that CB_2 receptor expression within the tumor microenvironment contributes to the exhaustion of CD8+ T cells and NK cells, thereby impairing antitumor immunity. Its deletion enhances the response to immune checkpoint blockade, positioning the CB_2 receptor as a potential immunosuppressive checkpoint receptor in cancer[239]. CB_2 receptor signaling in TAMs and MDSCs contributes to immune suppression in the tumor microenvironment. Activation of CB_2 receptor promotes M2-like polarization and enhances IL-10 and Arg-1 expression, thereby facilitating the recruitment of Treg cells and inhibiting CD8+ T cell responses[240–243]. Conversely, CB_2 receptor blockade or deletion reprograms these myeloid cells toward a pro-inflammatory phenotype, boosting antitumor immunity[244].

Furthermore, CB_2 receptor activation enhances the presentation of antigens by DCs, leading to more effective T-cell priming and clonal expansion[245,246–249]. Notably, CB_2 receptor functionally interacts with traditional immune checkpoint pathways. Activation of the CB_2 receptor inhibits the STAT3 and NF-κB pathways, which in turn lead to the downregulation of PD-L1 expression on both tumor and antigen-presenting cells[250,251]. Additionally, it influences the IL-6/IL-10 axis, which regulates PD-1 expression in T cells[252]. In murine models of lung carcinoma and melanoma, CB_2 receptor agonists have been shown to decrease the expression of PD-1 and TIM-3 on CD8+ T cells, restoring their cytotoxic function and granzyme B production. CB_2 receptor activation encourages a shift from Treg to Th1-like immune responses, thereby enhancing anti-tumor immunity[253–255].

CB_2 plays a dynamic role in shaping the tumor microenvironment, particularly by influencing the behavior of immune cells and the tumor's vascular landscape[256]. Activation of CB_2 can shift TAMs away from an immunosuppressive, M2-like state toward a more inflammatory, M1-like profile, which better supports immune activation[257,258]. This shift helps reduce the presence of Treg and boosts the recruitment and effectiveness of $CD8^+$ cytotoxic T cells, key players in anti-tumor immunity[257,259,260]. In tumors that typically exclude immune cells, often referred to as “cold” tumors, these changes can help break down barriers to effective immunotherapy. CB_2 also appears to regulate blood vessel growth by reducing levels of VEGF and related angiogenic signals, leading to more organized and less leaky vasculature[261,262]. This normalization of tumor blood vessels facilitates the entry and movement of immune cells through the tumor tissue.

Additionally, CB_2 influences the extracellular matrix by affecting enzymes such as MMPs and reducing TGF-β activity, thereby further improving immune cell access[263,264]. Some studies also suggest that CB_2 signaling can interfere with tumor cell proliferation by inhibiting growth factor pathways, such as EGFR and Ras[265,266]. Taken together, these effects position CB_2 not only as a target for controlling inflammation but also as a potentially valuable partner in cancer immunotherapy, especially in tumors that have been difficult to treat with checkpoint inhibitors alone. CB_2 receptor exists within a larger GPCR network involved in immune modulation. Importantly, CB_2 receptor counters immunosuppressive signals from adenosine A2A receptors (A2AR) and lysophosphatidic acid receptor 5 (LPAR5), both of which are associated with T-cell exhaustion. CB_2 receptor signaling mitigates A2AR-mediated suppression, thereby restoring mitochondrial function and glycolytic capabilities in T cells, which are key characteristics of sustained effector function[267–269].

Additionally, the CB_2 receptor influences intracellular calcium signaling and MAPK activation in DCs and CD8+ T cells, thereby bolstering immune surveillance[270–272]. In preclinical studies, selective CB_2 receptor ligands, such as JWH-133 and the phytocannabinoid BCP, have shown immunostimulatory and anti-tumor effects[140,272,273]. PAMs targeting CB_2 receptor further amplify these effects by making the receptor more responsive to endogenous ligands without disrupting normal signaling dynamics. Biased agonists that primarily activate MAPK or inhibit β-arrestin pathways present opportunities to fine-tune therapeutic responses and minimize side effects.

New delivery methods, such as tumor-targeted nanoparticles and liposomes that encapsulate CB_2 receptor agonists, are being developed to enhance bioavailability and reduce systemic exposure. These approaches are particularly relevant in solid tumors, where localized CB_2 receptor expression correlates with the disease severity. Although CB_2 receptor-specific drugs have not yet advanced to

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phase III clinical trials in oncology, early-phase studies and strong preclinical data suggest significant potential as a co-adjuvant with existing therapies. Stratification based on biomarkers will be crucial for patient selection and therapeutic optimization, which involves assessing CB_2 receptor expression levels, cytokine environments, and the types of immune cells present in the tumor microenvironment. CB_2 receptor appears to be a versatile, non-classical immune checkpoint receptor that reshapes the tumor-immune interface through various direct and indirect mechanisms.

11. Crosstalk Within the eCBome

The activity of CB_2 receptors within the growing concept of the eCBome does not function independently but collaborates with various signaling mechanisms, such as TRP ion channels, nuclear receptors, prostanoid pathways, and orphan GPCRs like GPR55 and GPR18[274]. This interconnected signaling framework captures the complexity of the roles of CB_2 receptors in immune modulation across both physiological and pathological conditions, including chronic inflammation, tumor immunity, and neuroimmune disorders.

One of the most significant interactions occurs between CB_2 receptor and TRPV1, a calcium-permeable ion channel that plays a vital role in pain signaling, oxidative stress, and immune response[275–277]. CB_2 receptor and TRPV1 are co-expressed in microglia, peripheral macrophages, and sensory neurons[278,279,280–285]. Evidence suggests that CB_2 receptor activation can mitigate TRPV1-driven neuroinflammation by reducing calcium influx, ROS generation, and the production of pro-inflammatory cytokines, such as IL-6 and TNF-α. Additionally, phytocannabinoids such as CBD and CBG, which exhibit weak binding to the CB_2 receptor, also act on TRP channels, displaying agonistic effects at TRPV1 and antagonistic effects at TRPM8, thereby enhancing the CB_2 receptor's contribution to an overarching anti-nociceptive and anti-inflammatory pathway[286–288]. In gastrointestinal disorders such as colitis and IBS, the combined modulation of CB_2 receptor and TRP channels improves epithelial barrier function, lowers neutrophil infiltration, and restores mucosal homeostasis.

The CB_2 receptor also exhibits a synergistic regulatory relationship with PPARγ, a transcription factor that regulates the expression of anti-inflammatory genes and mediates metabolic change[289]. Both endogenous and plant-derived cannabinoids, including AEA, palmitoylethanolamide (PEA), and oleoylethanolamide (OEA), interact with CB_2 receptor and PPARγ to shift macrophages toward the M2 phenotype, increase IL-10 levels, and inhibit NF-κB signaling[290–293,294–299]. In DCs, this dual engagement promotes a tolerogenic phenotype, reducing antigen presentation and encouraging Treg development. Remarkably, stimulation of CB_2 receptors has been shown to enhance PPARγ transcription and function in monocytes and immune cells residing in adipose tissue, highlighting its role in mitigating adipose inflammation and preserving insulin sensitivity. In microglia, the interaction between the CB_2 receptor and PPARγ supports neuroprotection by limiting excitotoxicity and facilitating the clearance of phagocytic debris.

Another significant aspect of CB_2 receptor crosstalk relates to the prostaglandin system, particularly the COX-2-dependent conversion of AEA and 2-AG into prostaglandin-ethanolamides and prostaglandin-glycerol esters[300]. CB_2 receptor activation indirectly suppresses pro-inflammatory pathways that drive COX-2 expression and prostaglandin E2 (PGE2) production, potentially modulating immune suppression mediated by EP2 and EP4 receptors [301–303]. In the tumor microenvironment, this modulation can diminish the recruitment of MDSCs and Treg-mediated tolerance while facilitating the reactivation of CD8+ T cells[304–307].

CB_2 receptor signaling interacts with orphan GPCRs such as GPR55 and GPR18, which share endogenous ligands with the CB_2 receptor[308,309]. GPR55 generally stimulates pro-inflammatory responses in monocytes, microglia, and cancer-associated fibroblasts[310–312]. Conversely, activation of CB_2 receptor counteracts GPR55-induced cytokine production, indicating a receptor-level antagonism that may shape immune tone[313,314]. GPR18, a receptor involved in resolution-phase signaling and the chemotaxis of CD8+ T cells, shows some overlap with the CB_2 receptor in immune tissues[315–318]. The coordination of CB_2 receptor and GPR18 may play a role in

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reprogramming macrophages and responses during wound healing, although pharmacological separation remains challenging due to ligand promiscuity[319–321]. Collectively, CB_2 receptor stands out as a crucial signaling hub within the eCBome, integrating immune, metabolic, and neuronal signals through various receptor interactions. Its actions in regulating immunity are amplified and refined through interactions with TRP channels, PPARs, prostanoid pathways, and orphan GPCRs, creating a dynamic network that can finely adjust inflammation and immune resolution. These interactions carry significant implications for therapeutic approaches targeting polypharmacological modulation, particularly in conditions characterized by overlapping inflammatory and metabolic origins, such as cancer, neurodegenerative diseases, and autoimmune disorders. Thoughtful drug design that acknowledges this complexity, rather than isolating CB_2 receptor signaling, holds significant potential for developing the next generation of cannabinoid-based immunotherapies.

Conclusions

This review provides a detailed and integrative examination of the CB_2 receptor, emphasizing its crucial role within the eCBome and its substantial contributions to immune regulation. Moving beyond the conventional perception of CB_2 receptor as merely a peripheral immune receptor, we emphasize its dynamic and inducible expression across a diverse array of immune cell types, including T lymphocytes, B cells, macrophages, dendritic cells, and microglia, and its context-dependent upregulation within neuronal and tumor microenvironments, underscoring its adaptability across immune and non-immune landscapes. CB_2 receptor is particularly notable for its inducible characteristics and the intricate regulatory frameworks that govern its expression, especially in the settings of immune activation, inflammation, and neuroimmune signaling. Its transcriptional control is finely tuned by a multilayered network of DNA- and RNA-based mechanisms, including promoter methylation, histone modifications, and the activity of non-coding RNAs. These epigenetic processes ensure CB_2 receptor expression is precisely modulated in response to physiological demands or pathological stress, enabling it to shape immune cell behavior and inflammatory outcomes with high specificity. Beyond transcriptional control, CB_2 receptor signaling exhibits functional versatility through mechanisms such as biased agonism, receptor dimerization, and interaction with complementary pathways, including TRP channels, PPARγ, prostanoid systems, and orphan GPCRs like GPR55 and GPR18. This signaling plasticity positions CB_2 receptor as a regulatory hub within the broader eCBome network. Framed within multiple pathological contexts, including autoimmune and inflammatory diseases, neuroinflammation, depression, chronic pain, schizophrenia, and cancer, this review highlights how CB_2 receptor modulates the immune landscape by promoting regulatory over effector responses, reprogramming macrophage and microglial phenotypes, altering cytokine profiles, and influencing cell trafficking.

While preclinical studies provide strong evidence for the therapeutic potential of CB_2 receptors, clinical translation faces several challenges, including species-specific differences in CB_2 receptor biology, limited pharmacological selectivity, and the absence of predictive biomarkers for patient stratification. Nonetheless, emerging strategies such as allosteric modulation, biased ligand design, and polypharmacological approaches, particularly the co-targeting of CB_2 receptor-PPARγ and CB_2-TRPV1, are paving the way for more precise and effective therapeutic interventions.

In summary, CB_2 receptor signaling offers a powerful and adaptable means of tuning immune responses, mitigating pathological inflammation, and maintaining immunological homeostasis. Our evolving understanding of its regulation at the epigenetic and signaling levels not only reshapes its pharmacological potential but also reinforces CB_2 receptor as a compelling candidate for next-generation therapies targeting immune-mediated and inflammation-driven diseases.

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Abbreviations

The following abbreviations are used in this manuscript:

The following abbreviations are used in this manuscript:

CB1: Cannabinoid Receptor Type 1

CB_2 / CB_2R: Cannabinoid Receptor Type 2

ECS: Endocannabinoid System

eCBome: Endocannabinoidome

GPCR: G protein-coupled receptor

TRPV1: Transient Receptor Potential Vanilloid 1

PPARs: Peroxisome Proliferator-Activated Receptors

GPR55 / GPR18: G protein-coupled receptors 55 and 18

AEA: Anandamide (*N*-arachidonoyl-ethanolamine)

2-AG: 2-arachidonoyl-glycerol

PEA: Palmitoylethanolamide

OEA: Oleoylethanolamide

BCP: Beta-caryophyllene

CBD: Cannabidiol

CBG: Cannabigerol

THC: Δ9-tetrahydrocannabinol

NAM: Negative Allosteric Modulator

PAM: Positive Allosteric Modulator

cAMP: Cyclic Adenosine Monophosphate

PKA: Protein Kinase A

NF-κB: Nuclear Factor kappa-light-chain-enhancer of activated B cells

MAPK: Mitogen-Activated Protein Kinase

ERK1/2: Extracellular Signal-Regulated Kinases 1 and 2

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PI3K/Akt: Phosphoinositide 3-kinase / Protein Kinase B

STAT6: Signal Transducer and Activator of Transcription 6

NRF-2: Nuclear Erythroid 2-Related Factor 2

AP-1: Activator Protein-1

RNS: Reactive Nitrogen Species

ROS: Reactive Oxygen Species

TLR: Toll-Like Receptor

CNS: Central Nervous System

DCs: Dendritic Cells

Tregs: Regulatory T Cells

Th1: Type 1 T helper cell

Th2: Type 2 T helper cell

Th17: Type 17 T helper cell

M1 / M2: Macrophage polarization states

IL: Interleukin (e.g., IL-4, IL-10)

IFN-γ: Interferon gamma

TNF-α: Tumor Necrosis Factor alpha

TGF-β: Transforming Growth Factor beta

CCR7: C-C Chemokine Receptor Type 7

CD80 / CD86 / MHC-II: Costimulatory molecules

NK cells: Natural Killer Cells

ILC2: Group 2 Innate Lymphoid Cells

MDSCs: Myeloid-Derived Suppressor Cells

TAMs: Tumor-Associated Macrophages

FLS: Fibroblast-like Synoviocytes

DNMTs: DNA Methyltransferases

TET enzymes: Ten-Eleven Translocation enzymes

AID: Activation-Induced Cytidine Deaminase

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APOBEC: Apolipoprotein B mRNA Editing Enzyme

MeCP2: Methyl-CpG Binding Protein 2

BER: Base Excision Repair

miRNA: MicroRNA (e.g., miR-139, miR-665)

SNPs: Single Nucleotide Polymorphisms

CpG: Cytosine-phosphate-Guanine

FAAH: Fatty Acid Amide Hydrolase

MAGL: Monoacylglycerol Lipase

NAPE-PLD: N-acyl Phosphatidylethanolamine Phospholipase D

DAGL: Diacylglycerol Lipase

COX-2: Cyclooxygenase-2

MMPs: Matrix Metalloproteinases (e.g., MMP-3, MMP-9)

Arg-1: Arginase-1

iNOS: Inducible Nitric Oxide Synthase

EAE: Experimental Autoimmune Encephalomyelitis

IBD: Inflammatory Bowel Disease

SLE: Systemic Lupus Erythematosus

MS: Multiple Sclerosis

RA: Rheumatoid Arthritis

MDD: Major Depressive Disorder

DRG: Dorsal Root Ganglion

OVA: Ovalbumin (used in asthma models)

TME: Tumor Microenvironment

VEGF: Vascular Endothelial Growth Factor

GI: Gastrointestinal

HPA: Hypothalamic-Pituitary-Adrenal (axis)

CNR2: Gene encoding CB_2R

CRP: C-Reactive Protein

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SSRIs: Selective Serotonin Reuptake Inhibitors

SNRIs: Serotonin-Norepinephrine Reuptake Inhibitors

TRPs: Transient Receptor Potential channels

TRPM8: Transient Receptor Potential Melastatin 8

PPARγ: Peroxisome Proliferator-Activated Receptor Gamma

PPARα: Peroxisome Proliferator-Activated Receptor Alpha

PPARδ: Peroxisome Proliferator-Activated Receptor Delta

EP2: Prostaglandin E2 Receptor 2

EP4: Prostaglandin E2 Receptor 4

NO: Nitric Oxide

ZO-1: Zonula Occludens-1

CRISPR: Clustered Regularly Interspaced Short Palindromic Repeats

mTOR: Mechanistic Target of Rapamycin

BDNF: Brain-Derived Neurotrophic Factor

GABA: Gamma-Aminobutyric Acid

GR: Glucocorticoid Receptor

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