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EDITORIAL

Endocannabinoid engagement of CB_2 regulates RSV-induced immunity

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Since its discovery in 1993, the peripheral cannabinoid receptor (CB_2) [1] has been identified as a critical regulator of immune homeostasis by mediating the anti-inflammatory and immune suppressive effects of endogenous cannabinoids. CB_2 is encoded by the *CNR2* gene, a single exon gene flanked by 3′ and 5′ untranslated regions. *CNR2* is located on chromosome 1, and the genetic locus that maps to *CNR2* has been implicated in susceptibility to various autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematous and type 1 diabetes [2]. This, in combination with the fact that CB_2 also mediates immune suppressive and anti-inflammatory effects of exogenous cannabinoids, have made it an attractive target for putative therapies aimed at dampening autoimmune diseases [3].

In the mid 2000s, it was discovered that *CNR2* had a common dinucleotide polymorphism (rs35761398) in which CAA is mutated to CGG, causing a Q to R amino acid change in the first intracellular loop (Q63R). This non-conservative substitution is not likely to affect ligand binding [4], but could affect intracellular signaling. Indeed, early studies demonstrated that peripheral blood mononuclear cells (PBMCs) induced to proliferate with anti-CD3 could be inhibited more readily by the endogenous cannabinoids 2-arachidonoylglycerol (2-AG) and N-arachidonoylglycine (NA-gly) in PBMCs derived from those with the Q variant as compared to the R variant [5]. A follow up study in which the R or Q variant was expressed in HEK293 cells demonstrated that inhibition of forskolin-stimulated cAMP was lower in cells expressing the R variant as compared to the Q variant in response to WIN55212-2 or 2-AG [4]. Together these data suggested that the Q63R mutant CB_2 is less functional, and/or less responsive following ligand engagement.

The Q63R CB_2 variant has now been examined in several populations of patients with autoimmune disease in order to determine if the GG allele and/or GG/GG homozygosity is overrepresented (i.e., the R variant). In Caucasian subjects with multiple sclerosis, rheumatoid arthritis, lupus erythematosis, or myasthenia gravis, the GG/GG or AA/GG genotypes were detected more often than the AA/AA genotype in all diseases, while control subjects expressed all genotypes [5]. Similar results were found in Italian children in which the Q63R variant was increased more than 6-fold in children with celiac disease [2]. Another group of Italian children with chronic immune thrombocytopenic purpura (ITP) had the R variant overrepresented as compared to controls [6]. These results were confirmed in a cohort of Egyptian children with ITP [7]. Finally, it was shown that the R variant was associated with increased rates of relapse in an Italian cohort of children with juvenile idiopathic arthritis [8].

In this issue of *Virulence*, Tahamtan and colleagues [9] investigated the expression of the wild type (Q variant) and mutant (R variant) forms of CB_2 in Iranian children (age range 1 – 22 months) with respiratory syncytial virus (RSV) infection. They found the R variant at a *lower* frequency for infants hospitalized for acute respiratory tract infections (ARTI). They also found the same pattern for RSV-positive patients, regardless of whether they were hospitalized. Thus, for children with ARTI, about half of which were RSV-positive, the Q variant is overrepresented [9].

Together these data demonstrate that the R variant, the CB_2 form that is less responsive to endocannabinoids, is overrepresented in autoimmune diseases. While this is the first study in which the allelic frequency between CAA and CGG for *CNR2* has been determined in a cohort of ARTI patients, the data show that the Q variant, the CB_2 form that is responsive to endocannabinoids, is overrepresented. Thus, these findings are consistent with the hypothesis that CB_2 plays a regulatory role in which endocannabinoids

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control the magnitude of the immune response. For those with autoimmune disease, the predominant form of CB_2 is less responsive to regulatory control by endocannabinoids, while in patients with ARTI, the predominant form of CB_2 is subject to endocannabinoid regulation, thereby potentially reducing the immune response against the virus [9].

Tahamtan and colleagues also paralleled the findings in the ARTI patient cohort with studies conducted with a mouse RSV model [9]. First, they determined that *Cnr2* expression was increased in bronchoalveolar lavage fluid (BALF) in response to RSV. Other studies in humans have also shown that CB_2 and/or *CNR2* expression is increased in gut tissue from celiac disease [2] or synovial tissue from rheumatoid arthritis [10] patients (although these studies did not distinguish which form of CB_2 they detected). Second, Tahatman, *et. al.,* found that treatment of mice with the CB_2-selective agonist JWH-133 suppressed RSV-induced immune responses in the lung, which correlated with modest, albeit not statistically significant, increases in viral load in BALF. In contrast, blockade of CB_2 with AM630 enhanced many of the RSV-induced immune responses and modestly decreased (again without significance) viral load in the BALF [9]. The observations in the RSV mouse model are consistent with previous studies using $Cnr1^{-/-}/Cnr2^{-/-}$ mice with A/PR8/34 mouse-adapted influenza. Influenza responses in $Cnr1^{-/-}/Cnr2^{-/-}$ mice were enhanced as compared to wild type mice, and exogenous cannabinoid treatment with Δ^9-tetrahydrocannabinol suppressed influenza-induced immune responses and increased viral load [11,12].

In summary, the study by Tahamtan and colleagues presents novel information about the genotype of CB_2 and its role in susceptibility to ARTI and RSV. This is important because there are few studies in which the effect of cannabinoids on RSV has been evaluated. Another strength of the study is that the data were obtained in an Iranian cohort, a relatively understudied population. Moreover, the human studies were paralleled with mouse RSV studies using CB_2-selective agonists and inverse agonists. Thus, the study by Tahamtan, *et. al.,* provide additional evidence that endocannabinoid engagement of CB_2 is a critical regulatory mechanism in the immune system [9]. However, consideration of all data from the aforementioned studies support the idea that a delicate balance exists in immune regulation by cannabinoids via CB_2. Development of CB_2-specific ligands as autoimmune therapies might not be as effective in those bearing the R variant, and for those fighting ARTI, CB_2 activation could alleviate RSV-induced lung pathology provided the immune response is not compromised to the point of increased viral load.

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