

The isoprenoid end product N6-Isopentenyladenosine inhibits inflammation in bronchial epithelial cells through modulating the NF κ B pathway

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N6-Isopentenyladenosine (iPA) is a cytokinin identified in plants but also present in a free form or as a modified nucleoside bound to selenocysteine tRNA in human cells. It is an adenosine modified by an isopentenyl chain which derives from dimethylallyl pyrophosphate (DMAPP), an intermediate of the mevalonate pathway. iPA is required for efficient translational decoding of selenoproteins, and can modulate a variety of biological processes including cell cycle progression, DNA synthesis and apoptosis (1). Recently, it has been shown that iPA can exhibit immunomodulatory and anti-inflammatory properties by activating NK cells and modulating cytokine production in a way depending on the concentration used (2). In order to further investigate the anti-inflammatory properties of iPA and its possible mechanisms of action, we analyzed its ability to inhibit TNF α -induced inflammation, either in normal human bronchial epithelial cells or in a model of exacerbated inflammation represented by bronchial cells derived from a Cystic Fibrosis (CF) patient bearing the Δ F508 mutation. Results showed that iPA inhibited IL-8 and RANTES release in both type of cells in a different manner. The analysis of the key enzymes of the STAT3 and NF- κ B signalling pathways showed that iPA decreased the phosphorylation of STAT3 enzyme and markedly increased the expression of the direct NF- κ B inhibitor, I κ B α . These results were corroborated analyzing directly the NF- κ B activity in HEK 293/T cells transfected with a NF- κ B reporter plasmid. In these cells, iPA was also able to decrease I κ B α levels. Of interest, we found that iPA also increased the expression of the antioxidant selenoprotein glutathione peroxidase only in CF cells. Altogether these data suggest that iPA can negatively regulate inflammation with a general mechanism of action involving the inhibition of NF- κ B pathway but also propose that, in the presence of an altered inflammatory response such as in CF disease, iPA might act by modulating expression and/or synthesis of glutathione peroxidase.

References

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Keywords

N6-isopentenyladenosine; inflammation; NF- κ B.