AMPK Activators as Novel Drug Candidates for the Treatment of Inflammatory Bowel Diseases

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Inflammatory bowel diseases (IBDs), mainly represented by ulcerative colitis and Crohn's disease, are chronic and idiopathic diseases of the digestive tract. They incidence and prevalence is raising significantly in both developed and developing countries, thus representing a major challenge for the worldwide healthcare systems. The pharmacological armamentarium for the treatment of IBDs is far from being satisfactory, as the therapeutic success of the available drugs is still limited. Accordingly, the development of novel and effective compounds is highly requested. In this context, the serine/threonine heterotrimeric kinase AMPK (adenosine monophosphate-activated protein kinase) seems a sound target to strike.

Known as the central hub of energy homeostasis in eukaryotic cells, AMPK contributes also to the modulation of immune/inflammatory cell functions. Actually, alterations in AMPK expression and/or activity play a key role in the pathophysiology of immune-mediated inflammatory diseases characterized by abnormal immune cell functions, like IBDs. Moreover, AMPK is able to improve intestinal health by enhancing para-cellular junctions, nutrient transporters, autophagy and apoptosis. Accordingly, AMPK activation represents a promising therapeutic strategy for the treatment of intestinal inflammatory disorders.[1]

Here we describe a novel heterocyclic derivative, developed as AMPK activator.[2]

Tested in C2C12 myoblast cell lines, our compound significantly increased AMPK activity, in a concentration-dependent manner, turning out to be more effective than the well-known activator acadesine (ACA). Moreover, assayed in a mouse model of acute DNBS-induced colitis, the novel heterocycle displayed a relevant anti-inflammatory efficacy, proving to ameliorate both systemic- and tissue-related inflammatory parameters like body and spleen weight, colon length, macroscopic damage, TNF and MDA levels. Also in this case, our compound turned out to be significantly more active that the known reference ACA, thus imposing itself as a novel and valuable drug candidate for the treatment of IBDs.

1. Séverine Oliviera, S.; Foretza, M.; Violleta, B. Promise and challenges for direct small molecule AMPK activators. *Biochem. Pharmacol*. **2018**.
2. F. Angelucci, L. Quattrini, V. Coviello, L. Antonioli, M. Fornai, C. Blandizzi, W.K. Oh, C. La Motta. Italian Patent Application, 102017000039329.