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Letter to the Editor

Comment on "Polydeoxyribonucleotide Exerts Therapeutic Effect by Increasing VEGF and Inhibiting Inflammatory Cytokines in Ischemic Colitis Rats"

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We read and highly appreciated the interesting article by Kim et al. [1], focusing on the potential therapeutic effects of polydeoxyribonucleotide (PDRN) as an ischemic colitis medical treatment. The colon is particularly susceptible to hypoperfusion and critical low-flow state precipitate to an often innate preexisting less developed microvasculature [2]. As a compensatory mechanism, in the first stage of the colonic hypoxic state, vascular endothelial growth factor (VEGF) and hypoxia-inducible factor-1α (HIF-1α) are induced, and they paracrinally act to preserve tissue from ischemic damage. By attempting to counteract the hypoxic condition, activation of adenosine A_{2A} receptors ($A_{2A}R$) occurs in a cooperative fashion with hypoxia, modulating the anti-inflammatory pathway and stimulating VEGF release [3]. PDRN, a specific ligand of $A_{2A}R$, further enhances the VEGF expression, triggering a downregulation of inflammatory cytokines and an inhibition of both intrinsic and extrinsic apoptotic machineries [4–5]. Moreover, PDRN acts with a "salvage pathway" through the cell internalization of PDRN-derived purine and pyrimidine, mostly where *de novo* synthesis of DNA is severely impaired by ischemic condition, allowing a rapid tissue recovery [6]. This bioactive natural compound turns out to have relevant therapeutic effects in a range of pathological conditions, for its tissue repairing, anti-ischemic, and anti-inflammatory properties [6].

In Kim et al. [1], the authors documented a PDRN ability in increasing VEGF expression, reducing the histological damage, downregulating anti-inflammatory responses, and modulating apoptosis through the interaction with adenosine $A_{2A}R$. In this regard, the effects of PDRN in the experimental model of ischemic colitis are abolished using DMPX, a specific adenosine $A_{2A}R$ antagonist. This observation minimizes the involvement of the "salvage pathway" in the mechanism of action of PDRN in ischemic colitis. Furthermore, considering the involvement of VEGF in the activation of adenosine $A_{2A}R$, we believe it could be advantageous to demonstrate the effect of PDRN on neoangiogenesis and microvessel density, which may result in an augmented oxygen supply and a subsequent balance of the apoptotic mechanism [3].

To date, one of the most important ongoing clinical PDRN applications is wound healing, in which it increases reepithelialization and tissue granulation, increases the production of VEGF and blood vessels, and reduces the infiltration of inflammatory cells and scar size [7, 8]. Furthermore, it has also been used to reduce neuropathic pain and brain damage, to heal tendon injuries, to contrast the effect of estrogen deficiency-induced osteoporosis, and with intratracheal instillation to reduce lung inflammation and injury [9].

In conclusion, we believe that the data of Kim et al. [1] are remarkable, and considering the safe profile of PDRN

also in humans, it could be useful to attempt a clinical randomized trial to verify the properties of this promising compound.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

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