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Regenerative Roles of the Cyclooxygenase-2 Pathway in Neovascularization and Stem Cell Regulation: A Brief Perspective from *In Vitro* and *In Vivo* Studies

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ABSTRACT

Cyclooxygenase-2 (COX-2) is a key enzyme in prostanoid production and is best known as a mediator of the inflammatory response. Beyond this well-established role, COX-2 also contributes to tissue regeneration by promoting neovascularization and supporting stem cell recruitment, proliferation, and differentiation. Despite this, research on harnessing the COX-2 pathway as a therapeutic tool, rather than solely as a target for inhibition, remains limited, presenting a promising avenue for future studies. In this review, we summarize current insights from both *in vitro* and *in vivo* models into COX-2 signaling in tissue regeneration, focusing on molecular mechanisms through which its downstream mediators, especially prostaglandin (PGE_2), regulate vascular formation, tissue growth, and stem cell function. We also briefly outline the dual nature of these processes, which can either facilitate repair or drive pathological outcomes, and discuss emerging strategies for achieving controlled therapeutic applications.

1. Introduction

Cyclooxygenase-2 (COX-2) is one of the most extensively studied enzymes in biomedical research. It is the inducible isoform of cyclooxygenase and serves as the key enzyme responsible for initiating prostanoid production, a class of lipid-based signaling molecules. Clinically, COX-2 is best known as the principal target of non-steroidal anti-inflammatory drugs (NSAIDs), which are widely used to treat pain, fever, and inflammatory conditions.[1]

Prostanoids, as the downstream products of COX-2, are essential regulators of diverse physiological and pathological processes, most prominently the inflammatory response. Some prostanoids act as pro-inflammatory mediators, while others exert anti-inflammatory effects. They modulate cytokine expression and influence macrophage differentiation. They also blood flow by controlling vasoconstriction and vasodilation, thereby facilitating immune cell recruitment. Dysregulated COX-2 activity has been implicated in a wide spectrum of diseases, including inflammatory and metabolic disorders, neurodegenerative conditions, and cancer. Consequently, the search for novel COX-2 inhibitors remains an active area of research.[2]

In addition to its established role in inflammation, the COX-2 pathway also contributes to tissue regeneration. Prostanoids promote cell proliferation, neovascularization, and vascular remodeling. They also regulate stem cell recruitment and differentiation. Evidence

for these regenerative functions has been reported in multiple tissues, including muscle, bone, skin, kidney, and the gastrointestinal system.[3,4,5,6,7,8,9] Harnessing the COX-2 pathway as a therapeutic agent, rather than solely as a target for inhibition, therefore represents a promising direction for future research.

In this review, we briefly examine the current knowledge of the COX-2 pathway in tissue regeneration. We also discuss a few potential strategies that may be employed for future application of these beneficial processes.

2. Methods

The literature search was conducted using PubMed as the primary database. Eligible studies were original research articles with titles containing the terms "COX-2" or "prostaglandin" in combination with at least one of the following: "regeneration," "repair," "healing," or "rejuvenation." Ony *in vitro* and *in vivo* studies using mammalian model were considered. The search was limited to articles published in English between 2015 and 2025. Studies outside this range were included when essential for providing foundational or historical context.

3. Overview of COX-2

3.1. Structure and function

Cyclooxygenase, also known as prostaglandin-endoperoxide synthase (PGHS), catalyzes the rate-limiting step in prostanoid synthesis. In this step, arachidonic acid (AA) is converted to prostaglandin H_2 (PGH_2). Three isoforms of COX have been identified. COX-1 and COX-2 are encoded by the *PTGS1* and *PTGS2* genes, respectively, while COX-3 is spliced from *PTGS1*.[10] *PTGS1* is located on chromosome 9, whereas *PTGS2* is located on chromosome 1.[11,12] All COX isoforms catalyze the same reaction. However, while COX-1 is generally considered to be constitutively expressed, COX-2 is mostly inducible.[1,2]

COX-2 is homodimeric. Each individual subunit includes three main regions: an N-terminal domain resembling epidermal growth factor (EGF), a membrane-binding domain (MBD), and a large catalytic domain located at the C-terminal. A signal peptide sequence located upstream of the EGF domain directs membrane localization; in COX-2, this peptide is 17–18 amino acids long. The EGF-like domain significantly contributes to the dimerization interface. COX enzymes are localized to the luminal surface of the endoplasmic reticulum (ER) membrane. They are also found on both the inner and outer leaflets of the nuclear envelope of the cell. Membrane association is mediated by the MBD, which spans residues 59–111 of human COX-2 (Figure 1). The catalytic domain contains two distinct active sites responsible for cyclooxygenase (COX) and peroxidase (POX) activities, respectively.[10]

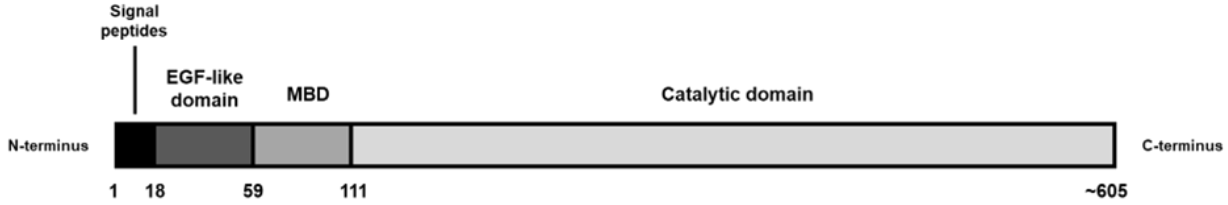

Figure 1. Putative domain structure of human COX-2 monomer. Following signal peptide cleavage, the mature COX-2 polypeptide consists of approximately 578 amino acids

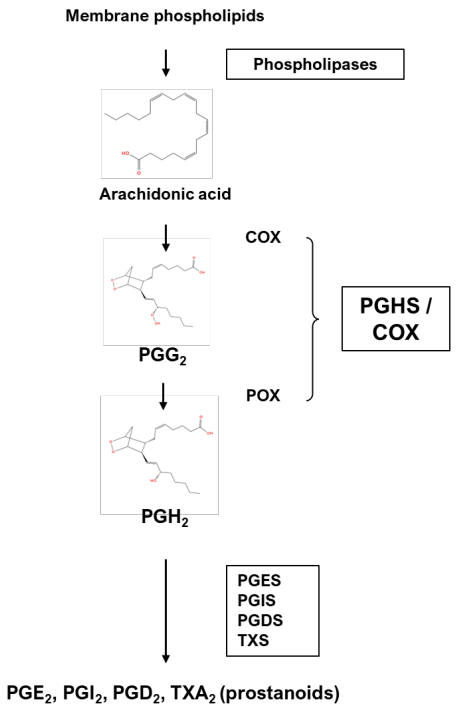

Figure 2. Prostanoid biosynthesis pathway. Each prostanoid is synthesized from PGH_2 using a distinct downstream enzyme. For example, prostaglandin E synthase (PGES) produces PGE_2, while prostaglandin I synthase (PGIS) produces PGI_2 by prostaglandin I synthase (PGIS). Chemical structures were generated using MolView

The precursor of AA is membrane phospholipids (Figure 2). Phospholipases, such as phospholipase A_2, act on membrane phospholipids, converting them into AA and subsequently releasing them into the cytoplasm. COX-2 then uses cytosolic AA to produce prostaglandin H_2 (PGH_2). The conversion of AA to PGH_2 occurs in two enzymatic steps. First, two oxygen molecules are incorporated into AA to form prostaglandin G_2 (PGG_2) during the cyclooxygenase reaction. This stage is followed by a peroxidase reaction, in which PGG_2 is reduced to PGH_2. PGH_2 then serves as a common precursor that is further metabolized by downstream synthases into a variety of bioactive lipid mediators collectively known as prostanoids, including the traditional prostaglandins, such as PGE_2, PGI_2, and PGD_2, as well as thromboxane (TXA_2).[10]

The functions of COX-2 and its end products are mostly studied in the context of inflammation. PGE_2 is primarily recognized as pro-inflammatory, inducing the expression of pro-inflammatory cytokines such as IL-6, IL-1β, IL-8, and TNF-α.[13,14,15,16,17] PGD_2 and TXA_2 are also largely proinflammatory. PGD_2 released by mast cells mediates allergic responses, increases local blood flow, and regulates mucus and Th2 cytokine production in the lungs. Inhibition of PGD_2 has been found to reduce inflammation in murine Krabbe's disease models.[18,19] TXA_2 induces platelet aggregation and vasoconstriction[20,21]. In contrast, PGI_2 is mostly anti-inflammatory[22]. In mouse astrocytes, PGI_2 was found to suppress TNF-α production induced by PGE_2.[16]

Each prostanoid typically signals through multiple, subtype-specific receptors, and the cellular response depends on which receptor is engaged. For example, PGE_2 acts through four receptors, EP1 to EP4.[23] Meanwhile, PGD_2 signals through DP1 and DP2 and can also stimulate the thromboxane receptor.[18] Furthermore, prostanoid receptors are G protein coupled receptors (GPCRs). Their coupling to different G proteins across cell types, together with cell type specific expression of downstream signaling molecules, adds substantial context dependence to COX-2 pathway

signaling. As a result, signaling through one receptor may promote regeneration, whereas signaling through another may exacerbate inflammation. Because of this complexity, a single compound is unlikely to be effective across all therapeutic settings.[23]

3.2. Regulation of COX-2

COX-2 expression is upregulated by various inflammatory stimuli. Pro-inflammatory cytokines, such as TNF-α, IL-1β, and INF-γ, upregulate COX-2 and its product PGE_2 in various tissues via the p38 mitogen-activated protein kinase (MAPK) and the c-Jun N-terminal kinase (JNK) pathway.[24,25,26,27,28] Bacterial pathogen-associated molecular patterns (PAMPs), such as lipopolysaccharide (LPS), induce COX-2 expression via toll-like receptor (TLR) 4.[29,30,31] Viral PAMP poly(I:C) has been reported to upregulate COX-2 via TLR3.[29] COX-2 expression can also be regulated by ROS; mainly mediated by NF-κB as well as MAPK.[32,33,34]

In addition to inflammatory stimuli, COX-2 is responsive to proliferative signals. Growth factors such as vascular-endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) induce COX-2 expression.[35,36,37] Transforming growth factor (TGF)-β1 and epidermal growth factor (EGF) work together to upregulate COX-2 expression.[38] COX-2 is also responsive to changes in oxygen level. Its promoter contains hypoxia-response elements (HREs), the binding site for hypoxia-inducible factor 1 (HIF-1).[39]

4. Roles of COX-2 in Tissue Regeneration

4.1. Neovascularization

One of the most critical functions of COX-2 in tissue regeneration is the promotion of neovascularization, and the most studied COX-2 end product in this context is PGE_2. Under normal physiological conditions, smooth muscle cells (SMCs) and endothelial cells (ECs) exhibit minimal proliferative activity. However, stimuli such as tissue injury, hypoxia, and inflammatory signaling can trigger these cells to re-enter the cell cycle. PGE_2 contributes to this response by inducing the expression of pro-angiogenic factors, thereby facilitating the formation of new blood vessels (angiogenesis) essential for tissue repair.[40]

For instance, bone marrow-derived cells (BMC) contribute to new vessel formation during ischemia and wound healing. They then migrate and differentiate into mature vascular endothelial cells at the site of injury. PGE_2 regulates these processes by binding to its receptor EP4 and activating AMPK.[41] Activation of EP2, together with EP4 to a certain extent, induces the expression of VEGF in human lung fibroblasts.[17]

PGE_2 has also been implicated in lymphangiogenesis. In a punched-hole wound model in mouse ears, maximal wound closure was accompanied by elevated COX-2 mRNA expression, followed by increased expression of VEGF receptor-3 (VEGFR-3) mRNA. In this context, PGE_2 did not directly stimulate lymphatic endothelial cell proliferation. Instead, it acted on infiltrating $CD11b^+$ macrophages within the wound granulation tissue, inducing the production of the pro-lymphangiogenic factors VEGF-C and VEGF-D via EP3 and EP4 receptor signaling.[42] A subsequent study by Hosono et al. demonstrated similar mechanisms during the healing of colitis in murine models.[3]

Other than PGE_2, there is evidence suggesting the role of PGI_2 in promoting angiogenesis. Binding of iloprost (an analogue of PGI_2) to the PGI_2 receptor (IP receptor) in the stromal cells of porcine endometrium, iloprost upregulated the mRNA expression of VEGF-A and FGF2.[43] However, in porcine endometrial endothelial (pEETH) cells, iloprost stimulated the transcription of VEGF-A receptor (*KDR*) and FGF2 receptor (*FGFR2*) rather than *VEGFA* and *FGF2* themselves.[44] Taken together, these findings indicate that the COX-2 pathway mediates neovascularization through distinct signaling pathways in different cell types.[40,42,43,44]

4.2. Stem cell regulation

In addition to its role in neovascularization, COX-2 contributes to tissue repair and regeneration by regulating stem cell development and function. In a mouse cranial defect model, implantation of COX-2 knockout muscle-derived stem cells (MSDCs) *in vivo* resulted in markedly reduced bone regeneration compared with implantation of wild-type (WT) MSDCs. MSDCs are multipotent cells capable of differentiating into myogenic, osteogenic, and chondrogenic lineages. COX-2 promotes these differentiation pathways by modulating the expression of chondrogenic and osteogenic markers, including phosphorylated SMAD1/5 (pSmad1/5) and osteocalcin.[6]

In murine mesenchymal stem cells (MSCs), COX-2 overexpression was reported to promote proliferation and migration via the extracellular signal-regulated kinase (ERK) and JNK pathway. Treatment with COX-2 inhibitor NS-398 suppressed MSC proliferation and promoted apoptosis. COX-2 overexpression has also been reported to promote MSC differentiation into cardiomyocytes by activating differentiation marker genes such as signal-regulatory protein alpha (*SIRPA*), NK2 homeobox 5 (*NKX2-5*), myosin heavy chain 6 (*MYH6*), and *MYH*.[8]

PGE_2 plays a critical role in skeletal muscle recovery mediated by muscle stem cells (MuSCs). In murine models, *in vivo* PGE_2 administration immediately after muscle injury increased the endogenous MuSC population at the injury site, thereby enhancing regeneration. Similar results were observed when injured muscles received stem cell therapy combined with PGE_2 delivery. Mechanistically, PGE_2 promoted MuSC expansion through EP4 receptor activation, which elevated intracellular cAMP levels and activated the transcription factor nuclear receptor–related 1 protein (NURR1). Loss of EP4 in MuSCs disrupted myofiber formation, underscoring the receptor's essential role in muscle repair.[45]

A recent groundbreaking study by Wang *et al*. demonstrated that short-term PGE_2 exposure administered alongside regular exercise reversed dysfunctions in MuSCs of aged mice. The study found that muscle injury normally activates regeneration through the PGE_2/EP4/cAMP/PKA/CREB pathway, but this process is impaired in aged MuSCs. Exogenous PGE_2 treatment restored this pathway and increased MuSC proliferation, yielding approximately 60% more cells compared with untreated controls.[46]

Furthermore, the same study demonstrated that exogenous PGE_2 reshaped chromatin accessibility in aged MuSCs, improving viability and suppressing necroptosis. In aged MuSCs, accessible chromatin is enriched for AP-1 and C/EBP motifs, whereas less accessible regions are enriched for E-boxes. Exogenous PGE_2 closed AP-1 sites and opened GC and CC E-box sites, a pattern that can influence MyoD-driven differentiation. Consistent with these changes, RNA-seq revealed that about 19% of PGE_2-responsive genes shifted toward youthful expression. PGE_2 also reduced AP-1 activity by lowering *JUN* and *JUND* expression, and it suppressed the necroptosis regulators *MLKL*, *RBCK1*, *CASP8*, and *CAV1*. [46]

4.3. Constraints and pathological effects

Although COX-2 possesses pro-regenerative functions, its effects are highly time-sensitive and injury-specific.[47,48,49] Activation of this pathway outside the appropriate temporal window, or in an unsuitable tissue environment, can drive pathological processes.[49,50]

For instance, in mouse models of bothropic venom–induced muscle injury, inhibition of COX-2 with lumiracoxib within the degenerative phase of injury (24 hours post-injury) exacerbated limb ischemia and local hemorrhage. Interestingly, COX-2 inhibition during the early regenerative phase (2 – 6 days post-injury) was found to enhance the synthesis of key pro-angiogenic molecules, such as VEGF and matrix metalloproteinases (MMPs), which are

essential for vascular remodeling in the later regenerative phase of muscle wound healing.[47]

In contrast, early-phase (days 3–7) COX-2 inhibition in a murine muscle contusion model reduced inflammatory cell infiltration and fibrotic area, with reduced TGF-β expression and α-smooth muscle actin (α-SMA)/TGF-β co-localization However, extending COX-2 inhibition into days 14–21 post-injury impaired tissue remodeling and fibrosis resolution.[48]

Another clear example of the dual role of COX-2 is its involvement in tumor development. In a transgenic mouse model, Kim *et al*. reported that deletion of 15-hydroxyprostaglandin dehydrogenase (15-PGDH), the enzyme responsible for degrading PGE_2, accelerated colon regeneration following experimentally induced colitis. However, PGE_2 also activates the oncoprotein Yes-associated protein (YAP) via the EP4/PKA/CREB signaling pathway. Persistent PGE_2 production, in conjuction with deletion of YAP inhibitor Sav-1, led to the formation of colon polyps by 12–16 weeks of age, which progressed to carcinoma by six months.[49]

Indeed, COX-2 is known to be overexpressed in cancer cells. Although it is not the main factor driving aberrant cell proliferation, the rapid growth and high cell density of tumor tissues create a hypoxic microenvironment that further induces COX-2 expression via HIF-1–mediated transcription. The resulting increase in prostanoid production promotes angiogenesis, supports tumor survival, and can enhance the migration and invasion of certain tumor cells.[50] The role of COX-2 in cancer development has been explored in-depth by a previous study.[51]

Collectively, this section highlights the role of the COX-2 pathway in neovascularization and stem cell regulation during wound healing. However, prolonged or excessive activation of COX-2, particularly in concert with other signaling pathways, may also promote tumor development.[49] Importantly, even within the same tissue, the type of injury can influence how COX-2 activity is regulated.[47,48] Figure 3 provides an overview of the pathways through which COX-2 and its products mediate regenerative functions.

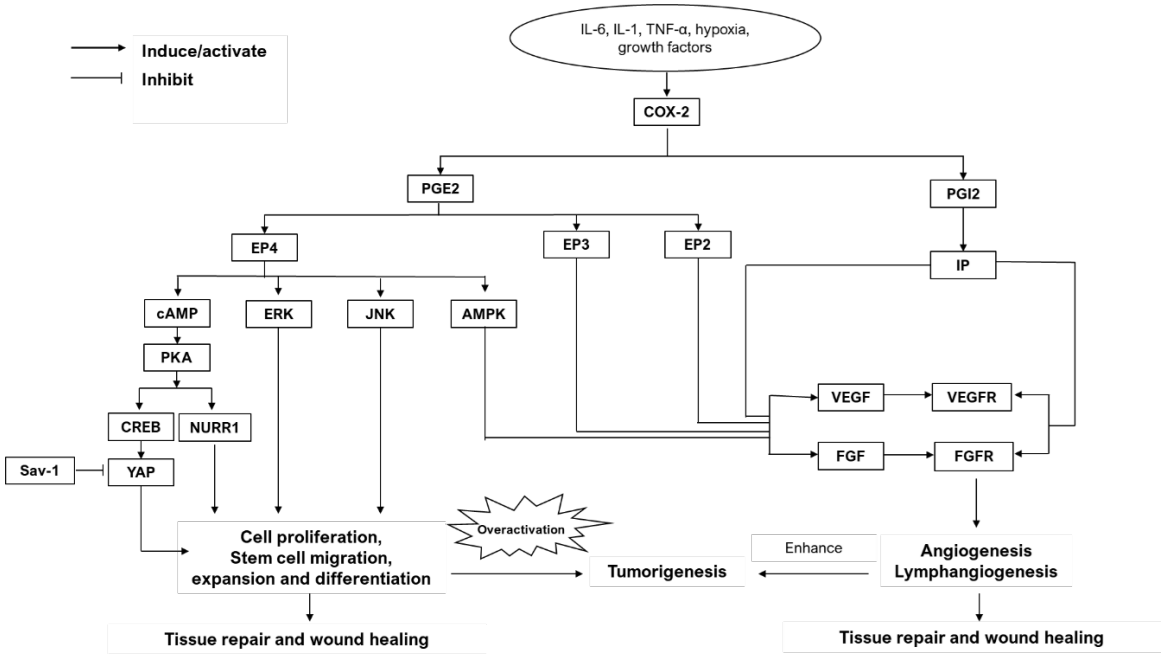

Figure 3. Overview of COX-2–mediated regenerative pathways. PGE_2 plays a critical role in tissue repair by activating its receptors EP2, EP3, and EP4, and regulates stem cell migration, expansion, and differentiation primarily through the EP4/PKA/CREB pathway. However, prolonged or excessive activation of this signaling, particularly when overlapping with oncogenic pathways, can contribute to tumor development. In addition, prostanoids promote tumor survival by supporting vascularization within the hypoxic microenvironment

To our knowledge, a more comprehensive literature and systematic review specifically investigating the regenerative function of COX-2 has not yet been conducted. Furthermore, it should be noted that most studies retrieved using our method are derived from musculoskeletal models and PGE_2. Conducting such a review is a necessary step to address this gap and further build a more structured framework for when COX-2 exerts beneficial effects.

5. Potential Application of the COX-2 Pathway in Therapeutic Strategies

The simplest approach to harnessing the COX-2 pathway therapeutically is through its downstream products. However, prostanoids are small lipid molecules, presenting challenges such as low solubility or short half-life.[4,52] Precise temporal and spatial control of their release is also required, as uncontrolled activity may be detrimental and contribute to chronic inflammation.[53,54,55] In this section, we discuss several strategies that have been explored to address this challenge.

15-deoxy-$\Delta^{12,14}$-prostaglandin J_2 (15d-PGJ_2) possesses anti-inflammatory properties and contributes to bone metabolism and regeneration, but its poor water solubility limits bioavailability. To overcome this, Qi et al. encapsulated 15d-PGJ_2 in poly(D,L-lactide-co-glycolide) (PLGA) nanocapsules, improving solubility and absorption. In a rat femoral defect model, nanocapsule delivery suppressed IL-6, IL-1β, and TNF-α more effectively than the free compound. Moreover, 15d-PGJ_2 nanocapsules enhanced mature bone formation by upregulating bone morphogenetic protein-6 (BMP-6), platelet-derived growth factor-B (PDGF-B), EphrinB2, and osteoprotegerin.[56]

Another strategy involves matrix-based delivery systems, in which bioactive molecules are embedded within a scaffold. Zhang and colleagues designed a chitosan hydrogel matrix both *in vitro* and *in vivo* to achieve controlled release of PGE_2. Using a mouse model of cutaneous wound healing, they demonstrated that the chitosan-PGE_2 hydrogel enhanced wound closure by promoting M2 macrophage differentiation and early angiogenesis through the upregulation of angiogenic factors and their receptors.[4]

Similarly, Huang *et al*. utilized a PGE_2-collagen matrix and successfully demonstrated that sustained and controlled exposure to PGE_2 improved neovascularization and skeletal muscle regeneration in a murine hindlimb ischemia model.[52]

Together, these findings suggest the potential of spatially and temporally controlled delivery of COX-2 end products. However, current evidence has not yet addressed the significant practical challenges of implementing these strategies. Further investigation is also required to optimize the timing, dosage, and delivery of COX-2–derived prostanoids in order to maximize regenerative benefits while minimizing adverse effects.

6. Conclusion

The COX-2 pathway facilitates regenerative processes across tissues, including neovascularization, vascular remodeling, and stem cell recruitment, expansion, and differentiation. Most notably, these processes are mediated by PGE_2 through the activation of EP4/PKA signaling. Combining prostanoid with nanocapsules or matrix-based scaffolds to achieve controlled release illustrates the opportunity to harness the COX-2 pathway for treatment of wound healing, rather than using it solely as a target for inhibition.

However, the regenerative functions of COX-2 are time sensitive and strongly dependent on injury context and tissue type. Prolonged or mistimed enhancement or inhibition can disrupt regenerative processes and worsen outcomes. Therapeutic strategies that modulate the COX-2 pathway should therefore be designed with careful attention to timing and tissue context. In addition, further studies across a broader range of tissues are

required, and deeper exploration of prostanoids beyond PGE_2 may uncover many applicative potentials.

7. Author Contribution

M.P. wrote the manuscript and prepared the figures, and S.D. supervised the manuscript writing.

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