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Potential therapeutic interventions via EP2/EP4 prostaglandin receptors

Potencjalne interwencje terapeutyczne poprzez receptory EP2 i EP4 dla prostaglandyn

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Summary

Prevention and treatment of pathological inflammatory processes requires application of various classes of immune suppressors, such as calcineurin inhibitors, steroids and non-steroid inhibitors of prostaglandin synthesis. However, each type of these immune suppressors causes less or more serious adverse side-effects. Exploration of the role played by prostanoids in the immune response and identification of functionally distinct prostaglandin E receptors (EP1-EP4) opened new perspectives in therapy of inflammation, autoimmunity and prevention of graft rejection. The EP4 receptor appeared to be an attractive target to affect manifestations of various pathological states by application of either agonists or antagonists of the receptor. This article presents a short overview of experimental approaches aimed at manipulation of signaling via EP2 and EP4 receptors that could have therapeutic utility.

Key words: **EP4 • PGE2 • inflammation • immune response**

Streszczenie

Do zapobiegania i leczenia procesów zapalnych stosuje się różnego typu supresory odpowiedzi immunologicznej, takie jak: inhibitory kalcyneuryny, steroidy i niesteroidowe inhibitory syntezy prostaglandyn. Niemniej jednak każda z kategorii tych leków obarczona jest działaniami niepożądanymi. Badania nad rolą prostanoidów w regulacji odpowiedzi immunologicznej oraz identyfikacja funkcjonalnie odmiennych receptorów dla prostaglandyny E2 (EP1-EP4) otworzyły nowe perspektywy w terapii stanów zapalnych reakcji autoimmunologicznych i zapobiegania odrzucania przeszczepów. Stosowanie agonistów lub antagonistów receptora EP4 prowadziło do zapobiegania różnych stanów patologicznych. Artykuł ten stanowi zwięzły przegląd eksperymentów ukierunkowanych na stymulację lub blokowanie receptorów EP2 i EP4, o potencjalnym znaczeniu w terapii.

Słowa kluczowe: **EP4 • PGE2 • zapalenie • odpowiedź immunologiczna**

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Abbreviations: **Bcl-xL** – B-cell lymphoma extra large, antiapoptotic member of Bcl2 family; **cAMP** – cyclic adenosine monophosphate; **COX** – cyclooxygenase; **EGF-R** – epithelial growth factor receptor; **EP** – receptor for prostaglandin E; **ERK** – extracellular signal activated kinase; **IFN-γ** – interferon gamma; **IL** – interleukin; **IP** – receptor for prostaglandin I; **LPS** – lipopolysaccharide; **MLC** – mixed lymphocyte culture; **MLR** – mixed lymphocyte reaction; **NF-kappa B** – nuclear factor kappa B; **PG** – prostaglandin; **rhBMP** – recombinant human bone morphogenetic protein; **TNF-α** – tumor necrosis factor alpha; **VEGF** – vascular endothelial growth factor; **WnT** – proto-oncogene coding for signaling cysteine-rich proteins.

Introduction

Long-term use of immunosuppressive drugs is associated with undesirable side-effects [12]. Calcineurin inhibitors, such as cyclosporine A and FK506, applied routinely to prevent allograft rejection, inhibit prostacyclin release, which leads to vasoconstriction, damage of epithelium and, consequently, to nephrotoxicity [53,69]. Harmful effects of calcineurin inhibitors may also occur on dermal application [31]. Steroids, on the other hand, interfere with normal functioning of the hypothalamus-pituitary-adrenal axis and their use in children is limited [36]. Non-steroidal inhibitors of prostaglandin synthesis, such as 5-aminosalicylic acid, used for treatment of inflammatory bowel disease, also cause side-effects [54].

In the light of recent literature, excessive application of prostaglandin synthase (COX-1 and COX-2) inhibitors is totally unjustified [55,72]. Even in tumor-bearing patients, strong expression of COX-2 was correlated with a much longer survival [38]. In animal models application of selective COX-1 and COX-2 inhibitors led to deterioration of allergic pulmonary inflammation [50] and atopic dermatitis [60]. On the other hand, it appeared that the anti-inflammatory action of the antifungal agent sertaconazole nitrate was associated with the p38-COX-2-PGE2 pathway [61]. Furthermore, COX-2 was implicated in the inhibition of inflammatory states by lowering ICAM-1 expression in human vascular smooth muscle cells [5] and, following elicitation by IL-17, in suppression of TNF-α-induced CCL27 chemokine production by keratinocytes [29].

A major step in understanding the complexity of interactions between prostanoids and the organism's cells was the first attempt of classification and characterization of prostanoid receptors as well as their agonists and antagonists [9]. Further studies enabled the identification of EP2 and EP4 receptors as targets for PGE2 inhibitory effects on lipopolysaccharide-induced tumor necrosis α production [40] and to understand their roles in regulation of inflammation [67]. This review presents the consequences of stimulating or blocking EP4 and EP2/EP4 receptors, which may have therapeutic benefit for amelioration of inflammatory disorders, autoimmunity, prevention of osteoporosis or graft rejection. The involvement of EP2/EP4 receptors in mediation of immunological and pathophysiological phenomena is summarized in Table 1.

The immune response

The regulatory roles of prostaglandins and cyclic nucleotides in generation of the immune response were demonstrated more than three decades ago [19,78,79]. However, more rapid progress in elucidation of the mode of action of prostaglandins in the immune response could only be achieved following identification of PG receptors. The investigators, using mouse lines devoid of each of the four EP receptors, and the mixed lymphocyte reaction as a model for the immune response, found that the suppressive effect of PGE2 was dependent on EP2 and EP4 receptors, where EP2 receptors inhibited T-cell proliferation, whereas both EP2 and EP4 receptors down-regulated cytokine production by macrophages as antigen-presenting cells [43]. The role of EP receptors was also confirmed in a model of lipopolysaccharide-treated mouse neutrophils where PGE2 inhibited TNF-α production by EP4 and partially EP2 receptors, whereas IL-6 production was enhanced via the EP2 receptor [76]. The suppressive effect of PGE2 via EP2 and EP4 receptors on the presenting cell function was further confirmed in the case of dendritic cells in which the expression of MHC (major histocompatibility complex) class II antigens was down-regulated but IL-10 production stimulated [17]. PGE2 was found, in addition, to inhibit expression of co-stimulatory molecules ICAM-1 and B7.2, induced by IL-18 in human peripheral blood monocytes [63], potentially suppressing initiation of the immune response. The effect involved the EP2/EP4-cAMP signaling pathway. It also appeared that PGE2 can inhibit growth of cell lines dependent on IL-2 and IL-4 [16,34] and this effect was also dependent on involvement of EP4 receptors. The universal role of EP4 receptors in inhibition of both types of the immune response was demonstrated by Okano and coworkers in a human model [47]. The authors generated antigen-specific Th1 and Th2 cell lines to PPD and Cry j 1 antigens expressing EP2, EP3 and EP4 but not EP1 receptors. First, they showed that PGE2 inhibited IFN-γ and IL-4 production by these cell lines, respectively, upon antigenic stimulation. Second, application of EP2 and EP4 receptor agonists suppressed activation of these cell lines upon stimulation via a cAMP-dependent manner. EP1 and EP3 receptor agonists were without effect. Third, PGE2 and EP2 receptor agonist inhibited IL-5 and IFN-γ production by peripheral blood mononuclear cells by both antigens. The investigators concluded that PGE2 suppressed both types of the immune response by the EP2/EP4 receptor signaling pathway.

Blood vessels, ischemia/reperfusion injury and platelet aggregation

PGE2 may have both vasodilatory and vasoconstrictor actions depending on the receptors involved [68]. The authors showed that vasodilation was associated with the EP4-cAMP signaling pathway whereas vasoconstriction was mediated by

Table 1. Involvement of EP2/EP4 receptors in regulation of selected pathological and physiological phenomena

Model	Effects associated with actions of EP2/EP4 agonist or antagonist	Reference
Immune response	• inhibition in MLR of T-cell proliferation	43
	• inhibition of TNF α and stimulation of IL-6 in LPS-stimulated neutrophils	76
	• downregulation of MHC class II antigens and stimulation of IL-10 in dendritic cells	18
	• inhibition of IL-18-induced ICAM-1 and B7.2 expression in human monocytes	63
	• inhibition of IL-2 and IL-4-dependent cell lines proliferation	16,34
	• inhibition of cytokine production by antigen-specific Th1 and Th2 cell lines	47
Blood vessels	• vasodilation	68
	• vasodilation and activation of NO synthase	22
	• angiogenesis	52
	• vasodilation of human middle cerebral artery/association with headache	10
Ischemia/reperfusion injury	• protection in myocardial ischemia/reperfusion injury	20,75
	• protection in cerebral ischemia	37
Platelets	• inhibition of platelet aggregation and thrombus formation	51
Allergy	• induction of cAMP in neutrophils	41
	• inhibition of eosinophil accumulation, degranulation and induction of apoptosis	59
	• inhibition of LPS-induced changes in nasal epithelium and airway epithelial cells	18
	• inhibition of chemotaxis of peripheral blood eosinophils	39
Gastrointestinal tract	• inhibition of dextran-sulfate-induced colitis in mice (proliferation of mononuclear cells from *lamina propria* and cytokine production of Th1 profile)	28
	• inhibition of histological symptoms in dextran-sulfate and indomethacin-induced colitis in rats	44
	• EP4 receptor agonist in clinical trial of ulcerative colitis	42
	• healing of indomethacin-induced small intestinal lesions	65
	• protective effect on gastric mucosa in ethanol-induced damage	21
Organ damage	• block of LPS-induced pro-inflammatory gene expression and lipid peroxidation in cultured microglia	57
	• regulation of the course of mouse experimental encephalomyelitis	11
	• antiapoptotic action in mouse primary hepatocytes	30
	• antiapoptotic effect in rat visceral glomerular epithelial cells	3
	• protection against a chemotherapeutic drug in Jurkat cells	15
	• stimulation of proliferation and melanogenesis in skin melanocytes	58
Arthritis	• reduction of hyperalgesia and paw edema in Freund's adjuvant-induced arthritis in rats	8, 48, 49
	• inhibition of differentiation and expression of Th17 cells and IL-23 production by activated dendritic cells	8
	• inhibition of LPS-induced TNFα production in peritoneal macrophages in the model of pristane-induced murine arthritis	1
Bone formation	• reduction of caspase 3 and 8 activities in rat bone osteogenic stromal cells	71
	• promotion of bone formation in mice *in vivo* and *in vitro*, restoration of bone mass in rats subjected to immobilization stress	77
	• increase of bone mineral density in a model of ectopic bone formation in mice	56
	• augmentation of bone volume and mineral deposition in osteopontin-deficient mice	30
	• restoration of bone mass in B16 melanoma-bearing mice	66
Transplantation	• inhibition of adhesion molecules expression and proliferation and cytokine production by T cells in a human model of MLC	64
	• prolongation of skin allograft survival in rats	13
	• prolongation of mouse cardiac allograft survival	45, 46

the EP3 receptor. Others demonstrated that PGE2-induced vasodilation, mediated by the EP4 receptor, triggered activation of endothelial nitric oxide synthase by de-phosphorylation of threonine at position 495 [22]. PGE2 and selective EP4 receptor agonists were also found to be implicated in the process of angiogenesis by induction of endothelial cell migration, tubulogenesis, ERK activation and cAMP production [52]. It was also suggested that blocking EP2 and EP4 receptors could be a therapeutic approach to overcome the side-effects of COX-2 inhibitors [24].

In a series of studies, PGE2 was shown to exert protective actions in ischemia-reperfusion injury in various organs via the EP4 receptor, being probably a consequence of vasodilation. Such a phenomenon was found in the case of experimental myocardial ischemia-reperfusion in mice [75] and rats [20]. Interestingly, the EP4 receptor was significantly up-regulated in mouse liver after ischemia-reperfusion injury [33], and EP4 receptor agonist markedly inhibited local expression of pro-inflammatory cytokines and adhesion molecules. In this study the application of the EP4 receptor agonist was surprisingly effective (80% survival versus death of 88% of control mice). Signaling via the EP4 receptor also proved protective in a mouse model of cerebral ischemia [37]. Thus, therapeutic intervention by activation of the EP4 receptor may be of advantage after stroke injury.

The ability of prostanoids such as prostacyclin and PGE2 to augment vasodilation may, however, cause headache in healthy volunteers [73,74]. Another study showed that vasodilation of the human middle cerebral artery was mediated by the EP4 receptor [10]. Nevertheless, administration of BGC20-1531, an EP4 receptor antagonist, did not diminish headache in a trial involving healthy volunteers receiving infusion of PGE2 [2]. The authors concluded that other EP receptors could be involved in this experimental model.

The EP4 receptor, present on human platelets, is also involved in inhibition of platelet aggregation and thrombus formation [51]. It also appeared that this effect was induced by PGE2 but not PGE1, which interacts with EP3 and prostacyclin receptors and not with EP4 [23]. Therefore, the overall effects of PGE2 on platelet function may be dependent on a balance between the pro-aggregation and anti-aggregation actions of PGE2 via EP3 and EP4 receptors, respectively.

Allergy

PGE2 levels in the pleural cavity of rats, sensitized and responding to ovalbumin, were directly correlated with the numbers of eosinophils in the pleural exudates [4]. In a human study on mild asthmatics exposed to allergen, inhaled PGE2, given immediately before inhaled allergen, attenuated the allergen-induced airway response, hyper-responsiveness and inflammation [14]. PGE2-induced apoptosis in developing neutrophils was mediated by inducible nitric oxide synthase leading to NO-dependent activation of the CD95L/CD95 pathway [27]. It was subsequently shown that human eosinophils express mRNA for EP2 and EP4 receptors, the expression of the latter was significantly higher, and an EP4 but not EP2 receptor agonist induced cAMP in neutrophils [41]. Yet in another study on human and animal eosinophils the authors demonstrated efficacy of EP2 receptor agonists in inhibition of eosinophil accumulation, de-granulation and in induction of eosinophil apoptosis [59]. Other studies showed that EP4 agonist proved effective in inhibition of LPS-induced changes in rat nasal epithelium and in cultured human airway epithelial cells [18] as well as in a model of chemotaxis involving human peripheral blood eosinophils [39]. A very recent, extensive study, applying isolated airways from various species (guinea pig, mouse, monkey, rat, human) clarified the controversy regarding the use of EP2 and EP4 receptors in PGE2-induced relaxation of trachea [7]. It appeared that the phenomenon was species-dependent, i.e. EP2 receptor-mediated relaxation was found in guinea pigs, mice and monkeys, whereas EP4 receptor was involved in rats and humans. The authors suggested that these species-dependent variations could explain the lack of bronchodilator activity in clinical studies using EP2 receptor agonists.

Inflammation of the gastrointestinal tract

Oral treatment of rodents with dextran sulfate leads to mucosal damage of the colon and represents a convenient experimental model of inflammatory bowel disease in humans. In a study on mice devoid of respective types and subtypes of prostanoid receptors only EP4 receptor-deficient mice developed colitis characterized by epithelial loss, crypt damage and aggregation of neutrophils and lymphocytes in the colon [28]. In wild type mice, administration of an EP4 receptor selective agonist (AE3-734) inhibited symptoms of severe colitis. Moreover, the EP4 receptor agonist suppressed the proliferation of mononuclear cells from colon *lamina propria* and Th1 cytokine production by these cells. In another study on rats it appeared that expression of EP4 receptor mRNA increased significantly after one week treatment with dextran sulfate, accompanied by pathological changes in the colon [44]. A selective agonist of EP4 (ONO-AE1-329), administered intracolonically to rats, decreased the symptoms of colitis. In another model of colitis, induced by dextran sulfate and indomethacin [26], a subcutaneous, daily administration of an EP4 receptor agonist (AGN205203) strongly diminished both external and histological symptoms of colitis. The efficacy of sulfasalazine, a pro-drug of 5-aminosalicylic acid, as compared with an EP4 agonist in the dextran sulfate sodium-indomethacin model of mouse colitis, was also investigated [25]. The authors showed that the EP4 receptor agonist, used at 500 × lower dose than sulfasalazine, was more efficacious in amelioration of colitis symptoms although sulfasalazine caused a more rapid reversal in weight loss. They concluded that the EP4 receptor agonist would be more suitable in the maintenance of remission whereas sulfasalazine would be better for induction of remission. Recently, an EP4 receptor agonist (ONO-4819CD) was applied in a clinical trial involving patients with mild to moderate ulcerative colitis refractory to 5-aminosalicylic acid [42].

An EP4 receptor agonist (AE-329) was also effective in the healing process of small intestinal lesions induced by indomethacin administration to mice [65]. The investigators found that the healing process was significantly inhibited by repeated treatment with indomethacin after appearance of the ulceration. That effect was mimicked by an EP4 receptor antagonist but reversed by AE-329. In addition, indomethacin down-regulated vascular endothelial growth factor expression (VEGF) and angiogenesis in the mucosa. The investigators concluded that endogenous PGE2 promoted healing of small intestine lesions by stimulating angiogenesis via up-regulation of VEGF expression as a result of EP4 receptor activation.

It was also found that PGE2 may have protective effects on gastric mucosa in ethanol-induced damage [21]. The protective effect was mediated by EP2 and EP4 receptors

and involved activation of cAMP and phosphatidylinositol 3-kinase pathways. Interestingly, in mice with HLC/ethanol-induced damage of gastric mucosa, infection with *Helicobacter pylori* appeared to be protective due to induction of PGE2 by the bacteria. A selective inhibitor of COX-2 synthesis (NS-398) abolished that protective effect, resulting in increases of TNF-α mRNA expression and infiltration of neutrophils [62]. On the other hand, selective agonists of EP1, EP2 and EP4 receptors, but not that of EP3, reversed the undesirable action of NS-398.

Organ damage

PGE2-EP4 receptor signaling may have also significance in protection of organs in various pathological states, as well as against cell apoptosis. Since the concentrations of PGE2 and TNF- α are elevated in the cerebrospinal fluid of Alzheimer's disease patients, the effect of PGE2 on cell viability of SH-SY5Y neuronal cells treated with TNF-α was studied [35]. The researchers found that PGE2 had a protective effect, preventing the cells from undergoing TNF-α-induced apoptosis and also by maintaining the intracellular level of beta-catenin, a main transducer of the WnT signaling pathway. In another report, the anti-inflammatory significance of EP4 signaling in brain innate immunity using LPS challenge *in vitro* and *in vivo* was investigated [57]. PGE2-EP4 receptor signaling resulted in block of LPS-induced pro-inflammatory gene expression and lipid peroxidation in cultured microglia and brain. Also in plasma, an EP4 receptor agonist lowered the levels of pro-inflammatory cytokines. It also appeared that PGE2-EP4 signaling had dual effects in mouse experimental encephalomyelitis [11] depending on the phase of the disease. The authors concluded that PGE2 facilitated generation of Th1 and Th17 cells redundantly, through EP4 and EP2 receptors during the immunization period, but inhibited penetration by these cells into the brain through the EP4 receptor.

EP4 receptor agonists were also demonstrated to be protective in injury of such vital organs as liver and kidney. In a model of mouse primary hepatocytes, expressing all PGE2 receptors, stimulation of the cells with PGEP4-A, EP4 receptor agonist, resulted in induction of expression of Bcl-xL and cyclin D1 proteins and phosphorylation of EGF-R and ERK [30]. The authors concluded that the EP4 receptor agonist might be a therapeutic agent for fulminant hepatic failure because of its anti-apoptotic and regenerative actions on hepatocytes. Others cultured a subclone of rat visceral glomerular epithelial cells, overexpressing inducible COX-2 in serum-deprived conditions to induce apoptosis [3]. The induction of COX-2 was correlated with increased PGE2 production and resulted in better cell survival. In addition, the survival kinase Akt was activated. The anti-apoptotic effect of COX-2 induction was reversed by a specific inhibitor of the EP4 receptor L-161982, indicating the importance of EP4 receptor signaling in that anti-apoptotic effect. On the other hand, inhibition of EP4 receptor-mediated protection against the chemotherapeutic drug camptothecin in human T-cell leukemia Jurkat cells may have utility in cancer therapy [15].

Exposure to ultraviolet (UVB) light results in an inflammatory response in the skin that is associated with PGE2 production. It was found [58] that PGE2 stimulated EP4 receptor signaling in melanocytes, leading to cAMP production. On the other hand, PGE2 interacting with EP3 receptors on melanocytes lowered cAMP levels. Apart from demonstration of cAMP increase, PGE2 also induced proliferation of these cells and increase of tyrosinase activity. Thus, opposite effects of PGE2 on EP3 and EP4 receptors regulate proliferation and melanogenesis in melanocytes.

Arthritis and bone formation

The EP4 receptor can also be a target for reducing symptoms of pain and inflammation in arthritis. In a monoarthritic model of rats, injected with complete Freund's adjuvant, application of EP4 receptor agonist ONO-AE1-329 into the joint reduced hyperalgesia and paw edema [49]. Agonists of EP4 and EP2 receptors were also efficient in reducing LPS-induced TNF-α production from LPS-treated peritoneal macrophages in a model of murine arthritis induced by pristane [1]. On the other hand, IL-6 production was strongly up-regulated. Agonists of EP1 and EP3 receptors were not effective. Other reports, however, demonstrated something opposite, i.e. advantageous applications of EP4 receptor antagonists in arthritis models. In adjuvant-induced arthritis in rats the EP4 receptor antagonist CJ-023,423 significantly inhibited paw swelling, inflammatory parameters, synovial inflammation and bone destruction [48]. These effects were comparable to those of rofecoxib, a selective COX-2 inhibitor. In other animal models, involving induction of arthritis in mice with collagen or glucose-6-phosphate isomerase, as well as in adjuvant-induced arthritis in rats [8], the EP4 receptor antagonist ER-819762 or anti-PGE2 antibody exhibited suppressive effects on the symptoms of inflammation, including pain. The antagonist also inhibited EP4 receptor-stimulated phenomena such as differentiation of Th17 cells and Th17 cell expansion as well as IL-23 secretion by activated dendritic cells. Thus, the discrepancies in the actions of agonists versus antagonists in the model of adjuvant-induced arthritis remain to be elucidated.

Prostaglandin E2, acting via the EP4 receptor, also plays a role in bone formation. A study on rats showed that repeated injections of PGE2 led to increased bone formation as measured by several parameters [70]. PGE2 treatment was associated with increased induction of EP4 receptor expression which was not abolished by pretreatment of rats with a COX-2 inhibitor, suggesting that inhibition of endogenous PGE2 was without effect on the anabolic effect of the exogenously administered PGE2. In another study the authors [71] evaluated the effect of PGE2 on growth and apoptosis of rat bone marrow osteogenic stromal cells. They demonstrated that PGE2, acting via EP4 receptors, increased the number of the cells and reduced the activity of caspase 3 and 8 in these cells. Other studies also confirmed beneficial effects of EP4 receptor stimulation on bone formation [77]. The investigators, using mice lacking each of four PGE receptor subtypes, found that infusion of PGE2 was not effective in promoting bone formation in EP4-deficient mice. Also, in culture of bone marrow cells, PGE2 induced formation of mineralized nodules. In addition, administration of EP4 receptor agonist to rats, subjected to immobilization stress or ovariectomy, restored their bone mass and physical condition.

In an experimental model of ectopic bone formation in mice, employing application of recombinant human bone

morphogenetic protein-2 (rhBMP-2), the EP4 receptor agonist ONO-4819 increased bone mineral density as compared to a control [56]. It was also found [30] that in osteopontin-deficient, but not in wild type mice, suboptimal doses of an EP4 receptor agonist (ONO-AE1-329) augmented bone volume and mineral apposition. On the other hand, administration of an EP4 receptor antagonist *in vivo* restored bone loss in B16 melanoma-bearing mice and in culture it suppressed the osteoclast formation induced by B16 cells [66], suggesting its utility in melanoma therapy.

Transplantation

Studies on the effects of PGE1 in an *in vitro* model of acute rejection, induced by IL-18 in human mixed lymphocyte culture, showed that the prostaglandin inhibited expression of adhesion molecules on monocytes, proliferation of T cells and production of IFN-γ and IL-12 by these cells [64]. The effects of PGE1 were dependent on stimulation of IP/EP2/EP4 receptors. The involvement of EP2-4 receptors was also demonstrated in immunosuppression by PGE2 of rat skin transplants [13], indicating that a coordinating signaling of three (EP2, EP3 and EP4) prostaglandin receptors was necessary for prolongation of graft survival. In another transplantation model of mouse cardiac allograft [45] the organ recipients were treated with agonists of EP receptors. It appeared that EP2 and in particular EP4 receptor agonists significantly prolonged allograft survival. In another study the efficacy of EP4 receptor activation in prolongation of heterotopic cardiac allograft was confirmed [46]. The authors also showed that the EP4 receptor agonist suppressed the production of inflammatory cytokines in this model by inhibition of NF-kappa B activity.

Conclusions

The review of representative studies in various models of immune response, inflammation, hypoxia, organ damage, autoimmunity, bone catabolism and transplantation revealed therapeutic utility of application of either agonists or antagonists of EP2/EP4 receptors. These encouraging results led recently to synthesis of new structures, currently in preclinical and pharmacokinetic studies, where agonism and antagonism could be achieved by minor modification of the basic structure [6]. Based on high selectivity of action and lack of proven side-effects, that class of drugs has a great potential to replace the hitherto used classical immunosuppressors.

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