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21 Molecular Targets to Alleviate Enteric Neuropathy and Gastrointestinal Dysfunction

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Abstract

Enteric neuropathy underlies long-term gastrointestinal (GI) dysfunction associated with several pathological conditions. Our previous studies have demonstrated that structural and functional changes in the enteric nervous system (ENS) result in persistent alterations of

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intestinal functions long after the acute insult. These changes lead to aberrant immune response and chronic dysregulation of the epithelial barrier. Damage to the ENS is prognostic of disease progression and plays an important role in the recurrence of clinical manifestations. This suggests that the ENS is a viable therapeutic target to alleviate chronic intestinal dysfunction. Our recent studies in preclinical animal models have progressed into the development of novel therapeutic strategies for the treatment of enteric neuropathy in various chronic GI disorders. We have tested the anti-inflammatory and neuroprotective efficacy of novel compounds targeting specific molecular pathways. *Ex vivo* studies in human tissues freshly collected after resection surgeries provide an understanding of the molecular mechanisms involved in enteric neuropathy. *In vivo* treatments in animal models provide data on the efficacy and the mechanisms of actions of the novel compounds and their combinations with clinically used therapies. These novel findings provide avenues for the development of safe, cost-effective, and highly efficacious treatments of GI disorders.

Keywords

Enteric neuropathy · Inflammatory bowel disease · Chemotherapy · Apurinic/apyrimidinic endonuclease/redox factor-1 (APE1/Ref-1) · High mobility group box protein 1 (HMGB1)

Enteric neuropathy associates with many gastrointestinal (GI) disorders and underlies symptoms of GI dysfunction, including inflammatory bowel diseases (IBD) and chemotherapy-induced toxicity.

More than 7 million people suffer from IBD worldwide. Current treatments include corticosteroids and immunosuppressive therapy, which cause severe side effects including liver toxicity and immunosuppression. Biological therapies have fewer side effects but require hospitalization and intravenous infusions. Most IBD patients undergo surgery during the course of the disease. About 40% of Crohn's disease patients require repeated surgeries to remove inflamed parts of the intestine. Many IBD patients end up with colostomy after the resection of the entire colon. Moreover, IBD patients are at a high risk of developing colorectal cancer [1]. Colorectal cancer (CRC) is the second most common cancer worldwide; it is often asymptomatic at the early stages, and, therefore, in most cases, it is diagnosed at the advanced stages, when the tumour penetrates through the wall of the GI tract and blood appears in the stool. If diagnosed at the early stages, resection surgery is followed by chemotherapy; if diagnosed at the later stages, chemotherapy is the main treatment and in the case of rectal cancer radiotherapy. All chemotherapeutic drugs currently used clinically have severe neurotoxic and GI side effects [17]. Peripheral sensory neuropathy and GI side effects, such as nausea, vomiting, diarrhoea and constipation, are the main reasons for the reduction of the dose of the chemotherapy and treatment cessation, which significantly reduces the efficacy of anticancer treatment. Traditionally it was accepted that the GI side effects are due to mucosal damage (mucositis) [30]. Although mucositis plays an important role in pathophysiology of chemotherapy-induced GI adverse effects, however, mucosa regenerates very fast, but these side effects last many years after the end of chemotherapy in cancer survivors [15], suggesting that not only mucosa but also other structures are also affected. Our studies in colon tissues from IBD and CRC patients demonstrate that chronic inflammation and chemotherapy cause functional and structural damage to the enteric nervous system (ENS) innervating GI tract, making enteric neurons a viable target for effective therapies to attenuate GI dysfunction [5]. Our previous studies found that oxidative stress is a major contributor to enteric neuronal damage and death induced by intestinal inflam-

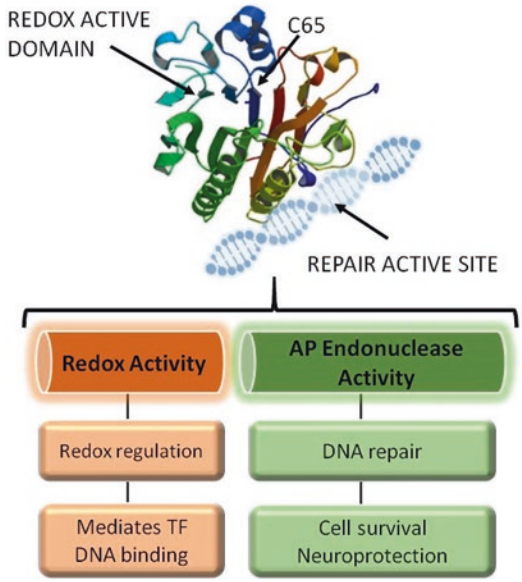

Fig. 21.1 APE1/Ref-1 is a vital dual functioning molecule containing a redox activating domain and a DNA repair domain

mation and platinum-based chemotherapeutic agent, oxaliplatin [11, 14].

One of the molecular targets identified by our studies is apurinic/apyrimidinic endonuclease/redox factor-1 (APE1/Ref-1). APE1/Ref-1 is a dual functional protein with endonuclease activity involved in the base excision repair (BER) pathway, which is critical for neuronal mitochondrial and nuclear DNA repair (Fig. 21.1). DNA repair is an important neuroprotective mechanism used for limiting neurotoxicity due to oxidative stress, direct toxicity and inflammation. APE1 also functions as a major reducing-oxidising (redox) factor that augments the binding of many transcription factors to DNA, including activator protein-1 (AP-1), nuclear factor kappa B (NF-κB), p53, the cAMP response element-binding protein (CREB), and hypoxia-inducible factor-1-α (HIF-1α), that play important roles in stress responses and various disorders [29, 32]. Professor Kelley's group is the first to identify that the repair function of APE1 contributes to the survival of non-dividing post-mitotic cells following oxidative DNA damage. Novel small-molecule compounds, APX3330 and its analogues, developed by Professor Kelley, directly and specifically inhibited APE1's redox signalling and enhanced DNA repair in dorsal root ganglia (DRG) neurons [7]. These compounds are highly effective in preventing or reversing cisplatin-induced sensory neuropathy without diminishing its anticancer efficacy [10]. Moreover, APX3330 demonstrated effective tumour-killing properties [26]. APX3330 is widely reported to be a direct, highly selective inhibitor of APE1 redox activity that does not affect the protein's endonuclease activity in tumours and enhances DNA repair in neurons. APX3330 is well absorbed orally with a bioavailability of >60%.

We hypothesised that using APX3330 in our animal models of IBD and chemotherapy, we will be able to block oxidative stress, prevent DNA damage and enhance DNA repair, which will alleviate enteric neuropathy and improve GI functions (Fig. 21.2).

We used the *Winnie* mouse model of spontaneous chronic colitis. These mice have a point mutation in the *Muc2* mucin gene (C57BL/6 background) leading to intestinal inflammation resulting from a primary intestinal epithelial defect [4, 8]. All *Winnie* mice develop mild spontaneous inflammation in the colorectum, which is developed in by 6–7 weeks of age (young adults) in pathogen-free conditions; it progresses over time and results in severe colitis by the age of 12–16 weeks. This is due to a thinner mucus layer allowing increased intestinal permeability and thus enhanced susceptibility to luminal toxins normally present within the gut. *Winnie* mice display symptoms of chronic diarrhoea, ulcerations, rectal bleeding and pain, as well as changes in microbiota composition similar to human IBD. Our RNA sequencing studies of the colons from *Winnie* mice demonstrate that this model accurately represents ulcerative colitis with 91% similarity in the expression of inflammation-associated genes, as well as 88% similarity to males with Crohn's disease. In comparison, 16.1% of genes in dextran sodium sulfate (DSS)-treated mice [6] and 12.5% in TNBS-treated rats

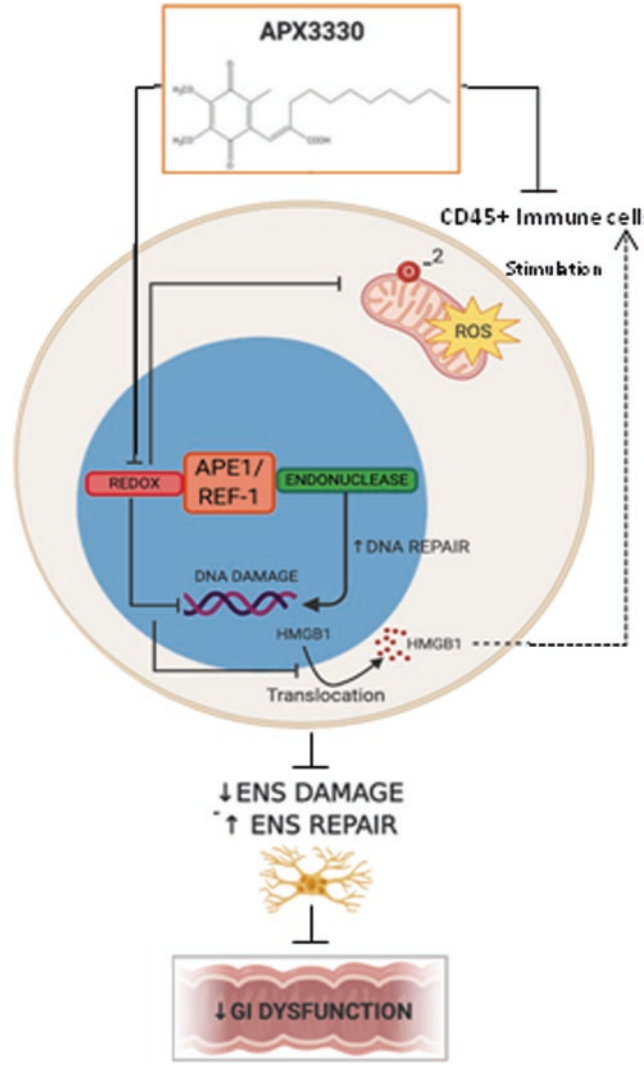

Fig. 21.2 APX3330 selectively inhibits APE1's redox signalling and DNA damage, reduces oxidative stress, alleviates enteric neuropathy, and reduces gastrointestinal dysfunction. (Created with Biorender.com)

[2] show concordance with IBD. Other models, including piroxicam-accelerated colitis in interleukin (IL)-10 knockout mice and adoptive transfer of CD4+CD25- leukocytes in immunodeficient mice, demonstrated a concordance of 77% and 64%, respectively, compared to 92 IBD-associated genes [9]. We have established the *Winnie* colony and published several papers on the characterisation of the enteric nervous system, gut functions and microbiota in this model [21–24]. Thus, the *Winnie* model of spontaneous chronic colitis closely represents human IBD and is not subjective to the variability of experimental techniques used to induce colitis.

Experiments were performed in 12 w.o (male and female) *Winnie* mice with active inflammation. APX3330 (25 mg kg^{-1} dissolved in 2% Cremophor, 2% EtOH and 96% sterile water) was administered twice a day with 8 h interval for 14 days via intraperitoneal injections. Sham-treated mice received the same volume and regimen of the vehicle solution. Age-matched C57BL/6 mice or non-*Winnie* littermates were used as naïve controls; no difference was found between them. The results demonstrate that APX3330 treatment had a significant positive effect on clinical symptoms in *Winnie* mice: it reduced rectal bleeding and rectal prolapse, alle-

viated diarrhoea and improved body weight in treated mice. APX3330 reduced inflammatory markers, a pan leukocyte marker, CD45, and faecal lipocalin-2 (Lcn-2), also known as neutrophil gelatinase-associated lipocalin (NGAL), which is a highly sensitive non-invasive biomarker of intestinal inflammation. APX3330 restored GI transit measured by in vivo X-ray imaging method and parameters of colonic motility measured ex vivo in organ bath studies of the excised colons from *Winnie* mice to control levels.

Winnie mice have significant damage to the enteric nervous system (ENS): reduction in numbers of nerve fibres projecting to the mucosa, loss of myenteric neurons and loss of enteric glial cells. APX3330 treatment increased density of nerve fibres, improved number of myenteric neurons and increased number of GFAP-positive glial cells in the myenteric plexus [25]. Overexpression of APE1/Ref-1 observed in the colonic cross section and the myenteric ganglia from *Winnie* mice, confirmed by immunohistochemical and western blot studies, was reduced by APX3330 treatment to the level comparable to control mice. Myenteric neurons from *Winnie* mice have a high level of oxidative stress measured by MitoSOX assay, which labels mitochondrial superoxide production. APX3330 reduced levels of MitoSOX fluorescence to control levels. DNA damage was measured by immunoreactivity to 8-Oxo-2′-deoxyguanosine (8-Oxo-dG), one of the major products of DNA oxidation widely used reliable marker of oxidative stress-induced DNA damage, and was observed only in the myenteric ganglia from *Winnie* mice, but not control mice and in APX3330-treated mice [25]. Another marker of the DNA damage used in this study is a high mobility group box protein 1 (HMGB1), a nuclear protein that acts as a chromatin-binding factor involved in the maintenance of nucleosome structure and regulation of gene transcription. HMGB1 is released by glial cells and neurons upon inflammasome activation [20]. HMGB1 is present in the nuclei of all enteric neurons; when neurons undergo cellular stress or injury, HMGB1 translocates from the nucleus into the cytoplasm and further into the extracellular space. This translocation was very prominent in the myenteric neurons of sham-treated *Winnie* mice. APX3330 inhibited this cytoplasmic translocation of HMGB1 in the myenteric neurons of *Winnie* mice.

Since HMGB1 is a downstream product of APE1/Ref-1 activation, we performed further studies testing the efficacy of HMGB1 inhibitor, a small-molecule compound glycyrrhizin, in two animal models: (1) chemotherapy treatment without colorectal cancer induction and (2) chemotherapy treatment in mice with an orthotopic model of colorectal cancer induced by implanting murine CT26 colorectal cancer cells into the caecum. Glycyrrhizin directly binds to a nuclear protein that maintains nucleosome structure and regulates gene transcription and has strong anti-inflammatory and neuroprotective properties. Inhibition of HMGB1 by glycyrrhizin modulates TLRs efficiently reducing the neuroinflammatory response resulting in neuroprotection from ischemic and traumatic brain damage [20]. It has been shown that HMGB1 inhibition reduces cisplatin-induced increases in iNOS levels and prevents ototoxicity [12], potentiates anticancer effects of platinum-based chemotherapeutics and has anticancer efficacy [31]. These properties make APX3330 and glycyrrhizin ideal candidates for the prevention and treatment of chemotherapy-induced enteric neuropathy.

Our previous studies demonstrate that treatment with first-line anti-colorectal cancer drugs, oxaliplatin, irinotecan and 5-fluorouracil induces death of enteric neurons, axonal damage, changes in their electrophysiological properties and significant morphological and functional alterations in neuronal nitric oxide synthase (nNOS)-immunoreactive neurons [3, 16, 18, 33]. Our studies provide evidence that oxidative stress is a key player in enteric neuropathy and colonic dysmotility associated with chemotherapy [14]. HMGB1 was observed within the nuclei of myenteric neurons from the control group. Our studies revealed that overexpression of HMGB1 and its translocation from the nuclei to cytoplasm were prominent in myenteric neurons from oxaliplatin-treated animals with and without

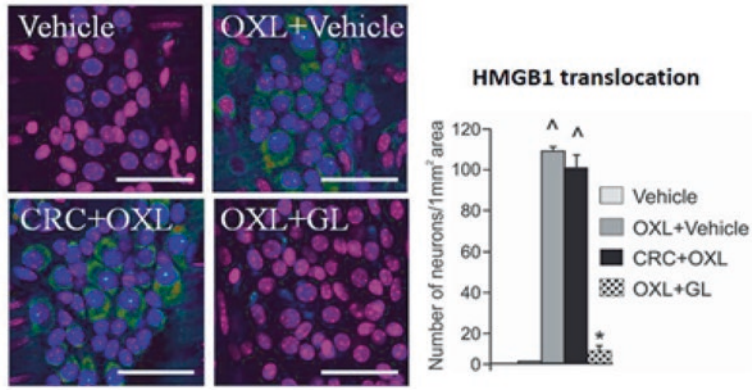

Fig. 21.3 Cytoplasmic translocation of HMGB1 (green) in myenteric neurons from mice oxaliplatin (OXL)-treated mice with and without CRC was prevented by co-treatment with glycyrrhizin (GL) (n = 6/group). ^$P < 0.0001$ compared to the control group, *$P < 0.001$ compared to OXL+Vehicle and CRC+OXL

colorectal cancer, but not in the neurons from untreated animals with colorectal cancer. HMGB1 translocated and released into the extracellular space acts as an antigen-presenting cytokine stimulating immune cells to release cytokines and chemokines, which activate toll-like receptors (TLRs), leading to changes in the microbiota [28]. These changes further exacerbate neuroinflammation and stimulate cellular damage and death of enteric neurons.

Both glycyrrhizin and APX3330 (25 mg/kg) combined with oxaliplatin were given to mice without cancer and in mice with CRC starting at day 7 post-surgery twice a day with 8 h interval for 14 days via *i.p.* injections starting on the same day as oxaliplatin treatment. The volumes for all injections were calculated to each animal's body weight with less than 200 μL per injection.

Co-treatment of glycyrrhizin (10 mg/kg) with oxaliplatin (3 mg/kg/dose; 3 times a week, 2 weeks) significantly reduced oxaliplatin-induced HMGB1 translocation in myenteric neurons (Fig. 21.3). The number of neurons in the myenteric plexus was not affected by induction of CRC and treatment with two vehicles. Treatment with oxaliplatin+vehicle in both mice with and without CRC induced loss of about 28% of myenteric neurons. The number of myenteric neurons in the CRC mice treated with oxaliplatin+glycyrrhizin was similar to the control group and significantly different to both oxaliplatin+vehicle-treated groups.

Co-treatment of glycyrrhizin and APX3330 with oxaliplatin inhibited tumour growth and vascularisation and prevented the loss of neurons induced by oxaliplatin treatment. These results provide a basis for further studies on the neuroprotective and anticancer efficacy of compounds targeting APE1/Ref-1 and HMGB1 proteins.

In summary, both treatments, APX3330 and glycyrrhizin, effectively alleviate enteric neuropathy and improve symptoms associated with intestinal inflammation and chemotherapy. APX3330 completed Phase I clinical trials for safety and toxicity in adult cancer patients who have failed all other treatments (NCT03375086) [27]. Clinical trials with glycyrrhizin have been approved by the World Health Organisation for the treatment of COVID-19 patients (ChiCTR2000029768 and ChiCTR2000030490) [13, 19]. Importantly, both of these drugs are not toxic and can be administered orally. Therefore, a fast translation of both compounds into clinical practice for the treatment of inflammatory bowel disease and the side effects of chemotherapy is plausible.

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Conflict of Interest Statement The authors declare no conflict of interest.

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