Inflammatory disease and sunlight: the vitamin D–poly (ADP-ribose) polymerase connection

Jon G Mabley[†] *&*
Csaba Szabo

[†]*Author for correspondence*
School of Pharmacy and Biomolecular Sciences, University of Brighton, Cockcroft Building, Lewes Road, Brighton BN2 4GJ, UK
Tel.: +44 127 364 2055;
Fax: +44 127 367 9333;
j.g.mabley@brighton.ac.uk

Environmental factors have long been suspected to affect the pathogenesis and incidence of inflammatory diseases. Epidemiological research has demonstrated that sunlight, or rather ultraviolet radiation exposure, is one such environmental factor that can affect inflammatory diseases. Increased exposure levels of ultraviolet radiation have been shown to decrease the incidence of autoimmune diseases – including rheumatoid arthritis, Type 1 diabetes, multiple sclerosis and colitis. The immunomodulatory effects of ultraviolet radiation are mimicked by administration of vitamin D, suggesting that photosynthesized vitamin D is the mediator involved in the biological effects of sunlight. Vitamin D has a variety of roles in the body, including regulation of the immune system predominantly affecting Th1 immunity, increasing T-cell apoptosis, reducing immune-cell infiltration, decreasing cytokine/chemokine production and suppressing proinflammatory transcription-factor activation and protein expression. Our group has provided evidence suggesting that vitamin D directly inhibits the activity of poly (ADP-ribose) polymerase, a multifunctional nuclear enzyme that also has a central role in regulating inflammation. Poly (ADP-ribose) polymerase inhibition also affects Th1 immunity in similar ways to vitamin D regulating transcription-factor activation, decreasing immune-cell infiltration and suppressing proinflammatory protein expression. Hence, inhibition of poly (ADP-ribose) polymerase by vitamin D may represent a novel mechanism for sunlight-mediated immunomodulation.

Sunlight

The apparent immunosuppressive/anti-inflammatory effect of ultraviolet radiation (UVR) has indicated that sunlight exposure may influence inflammation and the incidence of inflammatory diseases, such as rheumatoid arthritis (RA) [1], Type 1 diabetes [2], eczema/dermatitis [3], multiple sclerosis [2] and asthma [4]. It has been demonstrated that the incidence of RA, multiple sclerosis and Type 1 diabetes is affected to some degree by latitudinal gradient in the Northern Hemisphere, particularly in Western Europe and North America, with the prevalence of these disorders increasing at higher latitudes [5]. For example, the prevalence of RA in Europe increases from 0.3% in Italy to nearly 0.8% in Finland [1,6]. Seasonal influences have been observed on both disease incidence and clinical course, again suggesting UVR is an environmental player in the inflammatory process. UVR-mediated immunosuppression is related to a downregulation of cellular immunity, particularly affecting helper T cells, affecting a shift from Th1- to Th2-mediated processes [7].

Th1 immunity is considered proinflammatory and associated with increased production of the cytokines interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), interleukins (IL)-1, 6 and 12, chemokines macrophage inflammatory protein (MIP)-1α, MIP-2 and eotaxin, and reactive oxygen and nitrogen species, such as nitric oxide, superoxide and peroxynitrite [8,9]. Th1 immunity occurs in diseases of autoimmunity, such as RA [10,11], Type 1 diabetes [12,13] and multiple sclerosis [14], as well as in inflammatory diseases, such as colitis [15–17], septic shock [18] and adult respiratory distress syndrome [19]. Th2 immunity is associated with increased IL-4 and IL-10, which have anti-inflammatory effects and protect against inflammatory diseases, such as Type 1 diabetes [20]. Th2 immunity mediates immediate-type hypersensitivity to allergens [21], suggesting that UVR would exacerbate such reactions; however, no evidence of this has been observed and, in fact, studies have shown UVR to be beneficial for eczema and asthma [3,4]. The underlying mechanism for the immunomodulatory actions of UVR may be through photosynthesized vitamin D.

Vitamin D

Vitamin D is a seco-steroid, which can be chemically and enzymatically modified [22]. Seco-steroids are defined as those steroids in which one of the rings has been broken; in the case of vitamin D, by ultraviolet B radiation (sunlight). Vitamin D is metabolized sequentially in the liver and the kidney to its active form, calcitriol. Provitamin D is a four-member ring steroid with a side chain that

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identifies it as either ergosterol or 7-dehydrocholesterol [23]. During irradiation of provitamin D with UV radiation, the molecule absorbs a quantum of energy that allows ring opening, yielding a derivative known as previtamin D, which can undergo a thermo isomerization or photo isomerization to yield vitamin D. Once vitamin D is produced in the skin or absorbed from the diet it requires enzymatic conversion to form 1,25-hydroxyvitamin D_3 ($1,25[OH]_2D$), which, physiologically, is the most active form. This conversion was initially thought only to occur in the liver and kidney, but there is evidence now that a multitude of tissues have 1-hydroxylase activity, including the skin and immune cells, such as macrophages, T cells and dendritic cells, both of which can convert vitamin D to $1,25(OH)_2D$ [24].

The identification of vitamin D as an immunomodulator stems from three separate observations. First, vitamin D supplementation was shown to be anti-inflammatory and able to protect against numerous inflammatory diseases, including RA [25,26], Type 1 diabetes [27–29], inflammatory bowel disease [30,31], transplant rejection [32] and multiple sclerosis [33,34]. Second, vitamin D deficiency aggravates inflammatory and autoimmune diseases, including RA [35,36], Type 1 diabetes [37], inflammatory bowel disease [38] and multiple sclerosis [39]. Third, the vitamin D receptor (VDR) was discovered in the cells of the immune system, and it was also found that cells of the immune system, such as activated dendritic cells, can produce vitamin D [40].

The VDR was found on $CD4^+$ and $CD8^+$ T cells as well as macrophages, with receptor numbers increasing following immune-cell activation [41,42]. The VDR is a member of the steroid hormone receptor family, and upon ligand binding the VDR dimerizes with the retinoic X receptors, binds to DNA-response elements in promoters of vitamin D-responsive genes and modulates cell- and tissue-specific gene expression [43]. The degree of stimulation of vitamin D-responsive gene expression is influenced by the presence of an ensemble of coactivating or corepressing proteins, such as vitamin D receptor interacting proteins (DRIP). The genes affected by vitamin D activating the VDR are wide ranging, including those involved in the regulation of the cell cycle and proliferation, genoprotection, cell differentiation, vitamin D and calcium metabolism, and immunmodulation (reviewed in [44]). Vitamin D has nongenomic affects via membrane receptors associated with phosphate uptake, and has additional direct effects on enzymes, modulating their activity [45]. VDRs are also associated with the caveolae, where they are coupled to various second messenger systems, including phospholipase C, protein kinase C, G-protein-coupled receptors or phosphotidyl-inositol-3-kinase [46].

Vitamin D & immunomodulation

Vitamin D has been shown to be immunosuppressive/anti-inflammatory in a variety of cell types affecting immune cells directly, as well as other cell types regulating a variety of pro-inflammatory genes and proteins.

Vitamin D inhibits T-cell proliferation, particularly cells of the Th1 subset [47–49], as well as inducing $CD4^+$ T-cell apoptosis by increasing activation-induced T-cell death [50]. There are many proposed mechanisms by which vitamin D increases $CD4^+$ T-cell apoptosis. Identified mechanisms of vitamin D-induced T-cell apoptosis include: increased arginase expression with subsequent depletion of cellular arginine, causing inducible nitric oxide synthase (iNOS) to produce increased amounts of peroxynitrite, which is toxic to the T cell [33]; deprivation of T-cell survival signals [51]; and increased calpain-2 expression, which may convert T-cell receptor (TCR)-mediated calcium fluxes into death-inducing signals, as calpain-2 is a calcium-dependent protease implicated in triggering activation-induced T-cell death [52] and activation of caspase-3 and other cellular components of the apoptosis process [51]. Finally, vitamin D has been shown to inhibit the multifunctional nuclear enzyme poly (ADP-ribose) polymerase (PARP) [45], which has been linked to T-cell apoptosis in an animal model of Type 1 diabetes [53].

$1,25(OH)_2D$ regulates T-cell cytokine production inhibiting pro-inflammatory cytokines, as evidenced by reduced levels of IL-2, -8 and -12 and IFN-γ, while increasing levels of IL-4, -5 and -10 production [54,55], which, along with inhibition of Th1-cell proliferation, further shifts the T-cell response towards Th2 dominance. $1,25(OH)_2D$ inhibits the expression of IL-6, an important factor that stimulates Th17 cells, which are a critical part of the autoimmune reaction [56]. Recently, vitamin D has been shown to inhibit chemokine synthesis and monocyte trafficking both in Type 1 diabetes [57] and experimental autoimmune encephalomyelitis (EAE) [33]. Effects on transcription-factor activation affecting nuclear factor of activated T cells (NFAT), nuclear factor (NF)-κB and activator protein (AP)-1 may mediate the effects of vitamin D on cytokine

and chemokine expression and release. NFAT is a family of transcription factors that are pivotal for T-cell function, regulating a variety of immune processes, including T-cell proliferation and differentiation affecting IL-2, -3, -4 and -5, IFN-γ, TNF-α and MIP-1α expression [58], and has been identified as a target for immunosuppression [59]. $1,25(OH)_2D$ has been shown to suppress NFAT activation, and this may be a pivotal effect of vitamin D in terms of immunosuppression [60]. $1,25(OH)_2D$ has been shown to suppress chemokine expression in mesangial cells exposed to high glucose by preventing NF-κB translocation to the nucleus and reducing NF-κB binding [61]. The activation of NF-κB in dendritic cells is also inhibited by vitamin D [62–65], with c-Rel and RelB, protein members of the NF-κB family, being reduced in dendritic cells exposed to vitamin D in a VDR-dependent manner [62–65]. Inhibition of NF-κB in dendritic cells affects both their function and their maturation [66], explaining many of the immunomodulatory actions of vitamin D. $1,25(OH)_2D$ also inhibits TNF-mediated activation of NF-κB and AP-1 in human monocytes [67].

The effect of vitamin D on transcription-factor activation may explain the inhibitory effects of this hormone on proinflammatory proteins. Vitamin D suppresses nitric oxide formation both in macrophages and keratinocytes [68,69] – in macrophages, this is mediated by inhibiting the induction of the inducible isoform of nitric oxide synthase [68]. This effect, coupled with an inhibitory action on the T-cell expression of FasL [70], reduces the ability of the immune system to damage cells such as β-cells in diabetes. $1,25(OH)_2D$ inhibits cytokine-mediated expression of adhesion molecules, such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule (VCAM) (but not E-selectin) [71]. Therefore, vitamin D is capable of suppressing inflammatory cell infiltration by reducing adhesion-molecule expression and chemokine production. This may well result in an inhibition of the production of reactive nitrogen and oxygen species at the site of inflammation, thereby reducing cellular damage and further inflammation.

Vitamin D affects B cells by inhibiting antibody secretion and autoantibody production. $1,25(OH)_2D$ inhibits the differentiation of monocytes into dendritic cells [72], interfering with the T-cell stimulatory activity, and additionally blocking dendritic cell differentiation and subsequent IL-12 secretion [72], while promoting IL-10 secretion [73,74]. Vitamin D directly affects macrophages, modulating their ability to produce and release inflammatory cytokines and chemokines and decreasing their antigen-presenting activity by reducing the expression of major histocompatibility complex (MHC)-II molecules [75].

Overall, the most evident effects of vitamin D on the immune system are:

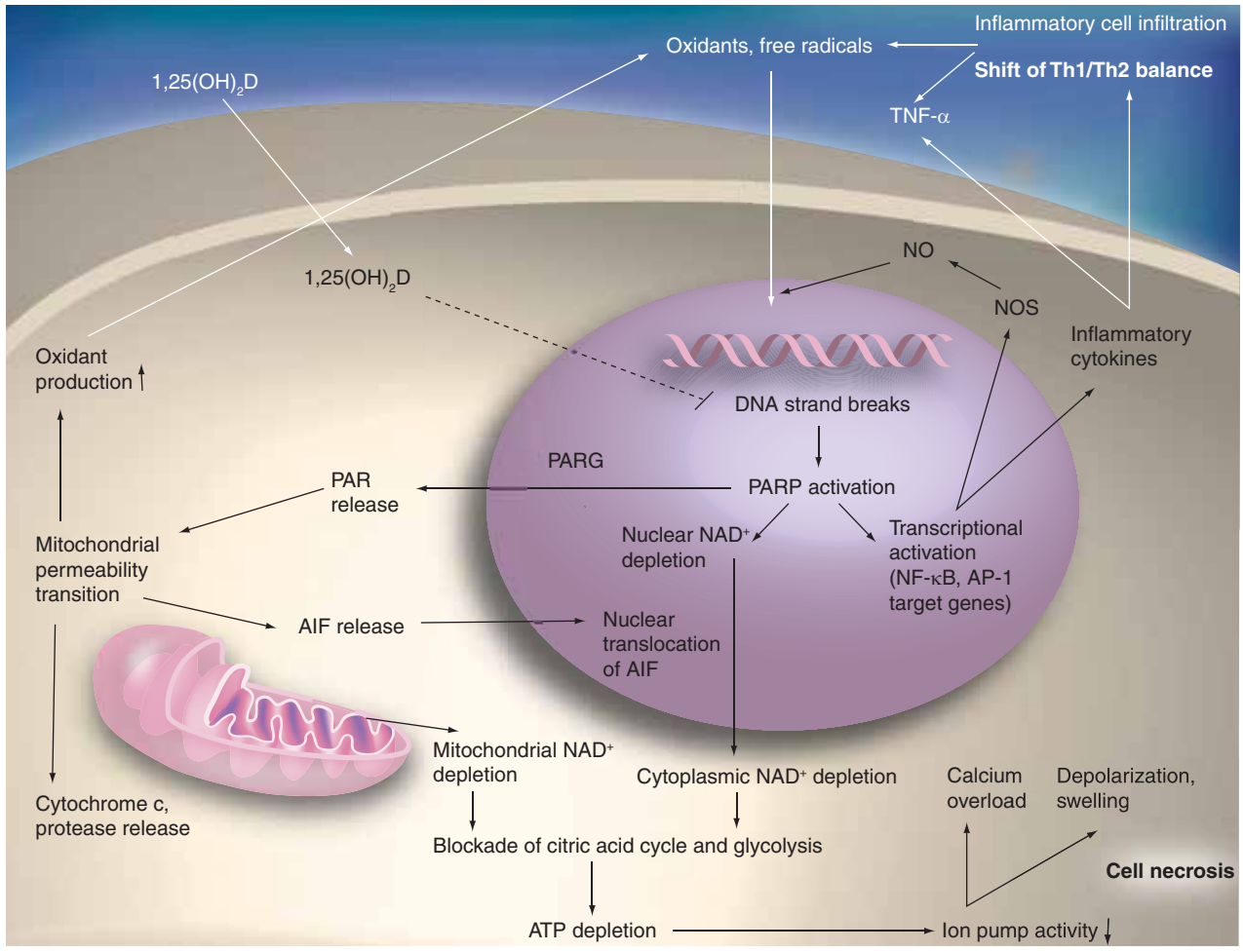
- Control of Th1 immunity
- Reduction of immune cell infiltration
- Inhibition of further inflammatory processes

Poly (ADP-ribose) polymerase

Poly (ADP-ribose) polymerase (PARP) is an enzyme abundantly present in the nucleus that modifies proteins by nucleotide polymerization [76]. The classic trigger for PARP activation is the presence of DNA single-strand breaks, which can be induced by a variety of environmental stimuli and free radical/oxidants, most notably hydroxyl radical and peroxynitrite [8]. In response to DNA damage, PARP becomes activated and, using nicotinamide adenine dinucleotide (NAD^+) as a substrate, catalyzes the building of homopolymers of adenosine diphosphate ribose units [77]. NAD^+ levels regulate an array of vital cellular processes: NAD^+ serves as a cofactor for glycolysis and the tricarboxylic acid cycle, thus providing ATP for most cellular processes. NAD^+ also serves as the precursor for NADP, which acts as a cofactor for the 'pentose shunt' for bioreductive synthetic pathways, and is involved in the maintenance of reduced glutathione pools [77]. Therefore, over-activation of PARP in pathophysiological conditions was shown to lead to catastrophic falls in cellular NAD levels and, subsequently, ATP levels, leading to cell dysfunction and death via necrosis. Additional research has indicated that PARP plays a role in many more cellular processes than previously thought, regulating cell death through apoptosis [78] as well as necrosis [79], gene transcription by affecting activation of transcription factors [80–82] and the activity of a variety of enzymes through ADP-ribosylation (Figure 1) [83].

PARP activation has been shown to occur in a wide variety of disease states including reperfusion injury and diabetic cardiovascular dysfunction [77]. PARP also plays a pivotal role in the pathogenesis of inflammatory diseases, such as colitis [84,85], diabetes [53,86], adult respiratory distress syndrome [19,87], septic shock [88] and autoimmune arthritis [11,89].

Figure 1. Schematic overview of poly (ADP-ribose) polymerase-mediated regulation of inflammation.



Inflammation-induced oxidant/free radical formation followed by DNA single-strand breaks activates PARP, leading to further inflammatory processes. PARP overactivation leads to cell necrosis, with release of cellular contents into extracellular spaces increasing inflammation. PARP regulates transcription-factor activation (NF-κB, AP-1 and NFAT), leading to inflammatory-cell activation (shift of Th1/Th2 balance), infiltration (MIP-1α, ICAM and VCAM) and cellular damage (iNOS and COX-2), all contributing to further inflammation.
$1,25(OH)_2D$: 1,25-hydroxyvitamin D_3; AIF: Apoptosis-inducing factor; AP-1: Activator protein-1; ICAM: Intercellular adhesion molecule; iNOS: Inducible nitric oxide synthase; NFAT: Nuclear factor of activated T cells; NF-κB: Nuclear factor-κB; NO: Nitric oxide; NOS: Nitric oxide synthase; PAR: Poly (ADP-ribose); PARG: Poly (ADP-ribose) glycohydrolase; PARP: Poly (ADP-ribose) polymerase; VCAM: Vascular cell adhesion molecule.

Poly (ADP-ribose) polymerase & inflammation

There are two pathways involved in the anti-inflammatory effects of PARP inhibition. The first pathway may be related to inhibition of necrotic and apoptotic cell death. Under basal conditions, PARP activity is relatively low and involved in repairing the DNA damage accumulated during normal cell function [90]. However, under conditions of oxidant stress, such as during inflammation, there are an increased number of DNA single-strand breaks, which the N-terminal domain of PARP recognizes, mediating a conformational change activating the C-terminal catalytic domain [90]. Activated PARP cleaves its substrate NAD^+ into ADP-ribose and nicotinamide, covalently attaching the ADP-ribose to various proteins, including an automodification to itself [90]. PARP then continues to attach ADP-ribose groups to the initial group, creating a branched nucleic acid-like homopolymer, poly (ADP) ribose [90]. The consequent reduction of cellular NAD levels and its effect on cell energetics decreases high-energy phosphate levels (ATP) and has deleterious consequences on a wide variety of cellular functions that can be substantially delayed from the time of oxidant exposure [90]. The severe energetic crisis resulting from PARP overactivation leads to

the triggering of the necrosis pathway of cell death [90]. Following the initial inflammatory oxidant insult and PARP activation resulting in necrosis, the release of the cellular contents into the extracellular space further triggers the inflammatory process. Inhibition of PARP in a variety of disease models has been shown to decrease the level of prenecrotic and necrotic cell responses induced by cytotoxic free radicals and oxidants produced during inflammation that, with the reduced spillage of cellular contents into the area, will further reduce inflammatory processes. More recently, PARP has been shown to regulate apoptosis through the release of apoptosis-inducing factor (AIF) [91], a pro-apoptotic flavoprotein residing in the mitochondrial intermembrane, which, once activated, relocates to the nucleus, causing chromatin condensation and large-scale DNA fragmentation [92]. The poly (ADP-ribose) (PAR) polymer is an identified signal to the mitochondria to release AIF [78], leading to induction of apoptosis.

The second group of mechanisms is related to the regulation of gene transcription by PARP and the subsequent impact on inflammatory and immune responses. Earlier theories of why PARP inhibition was protective in experimental models of disease focused on its effects on intracellular energetics, the resultant cellular dysfunction and cell death. However, over the last decade, *in vivo* investigations have revealed protective effects of PARP inhibition that are not associated with overt oxidant stress. These effects, observed in a wide variety of inflammatory conditions, relate to an effect of PARP on the expression, activation and nuclear translocation of key proinflammatory genes and proteins. Inhibition of PARP, either pharmacologically or through genetic absence, suppresses the activation of MAP kinase [93], the AP-1 complex [80] and NF-κB [94,95], which subsequently interferes with the expression of proinflammatory genes. Proinflammatory genes that have been affected by PARP inhibition include: enzymes (e.g., iNOS) [96], cyclooxygenase (COX)-2 [97], matrix metalloproteinases [77], adhesion molecules ICAM-1, E-selectin and VCAM [97–99], cell-surface proteins (such as integrins [CD11a]) [97,100], chemokines (e.g., MIP-1α and MIP-2) [11,19,94,101] and cytokines (e.g., IL-1β, IL-6 and TNF-α) [11,81,94,102]. PARP has been shown to poly(ADP-ribosyl)ate the T-cell transcription factor NFAT [103], which, as mentioned earlier, is pivotal in T-cell function, has been identified as a target for immunosuppressive therapies, and may play a crucial role in the anti-inflammatory effects of PARP inhibitors on immune cells affecting proliferation, infiltration and cytokine/chemokine production [58,59,104].

The combination of PARP inhibitors blocking both cell necrosis/apoptosis and inflammatory gene expression reduces neutrophil infiltration, proinflammatory cytokine levels and further generation of oxidant species in animal models of inflammatory disease. The overall effect of PARP inhibition in inflammatory diseases is to reduce Th1 immunity.

Vitamin D & poly (ADP-ribose) polymerase

Vitamin D and PARP inhibitors share similarities both in the diseases that they can protect against (Table 1) and in their immunomodulatory effects (Table 2), which formulated a hypothesis that vitamin D in some way inhibits PARP. In 2007, we reported that vitamin D had a novel pharmacological effect as a PARP inhibitor and demonstrated that it was the active form of vitamin D, $1,25(OH)_2D$, that is responsible for this action, with the monohydroxylated forms of vitamin D and the parent compound having little or no PARP-inhibitory activity [45]. The inhibitory effect of $1,25(OH)_2D$ on PARP was shown to be a direct effect on the enzyme, as the inhibition was observed in a cell-free assay that utilized the isolated human PARP enzyme [45].

Table 1. Protective effects of sunlight, vitamin D and poly (ADP-ribose) inhibition against human disease states.

Disease	Sunlight	Vitamin D	PARP inhibitors
Rheumatoid arthritis	+ [2,5,6]	+ [26,111]	+ [11,89,112]
Type I diabetes	+ [2,5,113,114]	+ [27,28,57,115]	+ [53,86]
Multiple sclerosis	+ [2,5,22,114]	+ [33,51,107,116]	+ [14,117,118]
Colitis	–	+ [30,31,47]	+ [84,119,120]
Endotoxic shock	–	+ [121]	+ [18,101,120,122–126]
Cardiovascular disease	+ [22,127]	+ [127,128]	+ [77]
Cancer	+ [129,130]	+ [22,43,131,132]	+ [133,134]

+: Protective effect; –:No protective effect; PARP: Poly (ADP-ribose) polymerase.

Table 2. Immunomodulatory effects of vitamin D and poly (ADP-ribose) polymerase.

Immunomodulatory action	Vitamin D	PARP inhibition
Immune cell infiltration	Decrease [33]	Decrease [19,94,101,135]
T-cell proliferation	Inhibit [136]	Inhibit [137]
T-cell apoptosis	Increase [33,50,54]	Increase [53]
Th1 cytokines	IL-1↓ [55,138] IL-2↓ [41,138] IL-6↓ [55] IL-8↓ [55] IL-12↓ [54,72,139,140] TNF-α↓ [55,138] IFN-γ↓ [41,138]	IL-1↓ [18,19,135,141] IL-2→ IL-6↓ [19,98] IL-12↓ [19,142] TNF-α ↓ [135] IFN-γ↓ [53,143]
Th2 cytokines	IL-4↑ [41,144] IL-5↑ [138] ↓ [41] IL-10↑ [54,138]	IL-4→ IL-5↓ [145] IL-10↑ [11] ↓ [142]
Chemokines	MCP-1↑ [27,146] MIP-1α↓ [30] MIP-1β↓ [27,33,57] MIP-2→ Eotaxin↓ [33]	MCP-1→ MIP-1α↓ [19,101] MIP-1β→ MIP-2↓ [11,19,101] Eotaxin↓ [147]
Transcription factors	NF-κB↓ [61,67,148] AP-1↓ [67] NFAT↓ [60,149]	NF-κB↓ [81,94] AP-1↓ [80,119] NFAT↓ [103]
Proinflammatory protein expression	iNOS↓ [68] COX-2↓ [150] ICAM↓ [71] VCAM↓ [71] E-selectin→ MHC II↓ [54,75]	iNOS↓ [96,151] COX-2↓ [97] ICAM↓ [97–99, 152] VCAM↓ [98,99] E-selectin↓ [98,99] MHC II↓ [143]

AP-1: Activator protein-1; COX: Cyclooxygenase; ICAM: Intercellular adhesion molecule; IFN: Interferon; IL: Interleukin; iNOS: Inducible nitric oxide synthase; MCP: Monocyte chemoattractant protein; MHC: Major histocompatibility complex; MIP: Macrophage inflammatory protein; NFAT: Nuclear factor of activated T cells; NF-kB: Nuclear factor-kB; PARP: Poly (ADP-ribose) polymerase; TNF: Tumor necrosis factor; VCAM: Vascular cell adhesion molecule.

The cellular implications for vitamin D inhibiting PARP, particularly of immunomodulatory processes, are summarized in Figure 1.

The literature on the immunomodulatory effects of vitamin D has indicated a possible role for the VDR, with VDR-knockout animals having increased susceptibility to immunological conditions, such as colitis [30]. However, VDR knockout has either no effect [105] or reduces the incidence of Type 1 diabetes [106] and reduces the incidence of multiple sclerosis [107] in experimental models. These observations appear to both contradict and support vitamin D exerting anti-inflammatory effects through a direct inhibition of PARP. Activation of PARP has proved central in both Type 1 diabetes [53] and multiple sclerosis [108], and the absence of the VDR having no effect or reducing disease incidence [105,107] suggests that the basal effect of vitamin D is either unaffected, or the lack of VDR-binding vitamin D increases free vitamin D levels, allowing an increased PARP inhibitory effect suppressing the inflammatory process. However, whereas there are discrepancies in the VDR-knockout models and the effect on inflammatory conditions, no such discrepancy is observed with vitamin D deficiency, which has been shown to exacerbate both inflammatory and autoimmune conditions [35–39]. The proinflammatory effects of vitamin D deficiency may be related to the lack of endogenous PARP inhibition by vitamin D, as well as its other well-documented immunomodualtory activities.

The data from the VDR-knockout animal having increased incidence of colitis [30] may not contradict the hypothesis that vitamin D directly inhibiting PARP activity partially mediates the immunomodulatory effects. The VDR itself may play an important role in regulating PARP activity, as PARP interacts with nuclear hormone receptors including those for steroids (estrogen),

Executive summary

Sunlight

- Ultraviolet radiation (UVR) exposure influences the incidence of inflammatory diseases.
- The incidence of inflammatory diseases is affected by latitudinal gradient and seasonal changes.
- UVR causes a shift from Th1- to Th2-mediated processes.

Vitamin D

- 1,25-hydroxyvitamin D_3 (1,25$[OH]_2$D) is the active form of vitamin D.
- 1,25$(OH)_2$D interacts with the vitamin D receptor (VDR), causing translocation to the nucleus to exert genomic effects.
- VDR on caveolae can activate phospholipase C, protein kinase C, G-protein-coupled receptors or phosphotidyl-inositol-3-kinase.
- VDR is found on many cell types, including immune cells.
- VDR activation results in genomic effects regulating the cell cycle and proliferation, genoprotection, cell differentiation, vitamin D and calcium metabolism and immune system activation.

Vitamin D & immunomodulation

- Vitamin D is immunosuppressive, affecting Th1 immunity by inhibiting T-cell proliferation and stimulating T-cell apoptosis.
- Vitamin D shifts the T-cell response from Th1 towards Th2, inhibiting Th1 cytokine/chemokine production (IFN-γ, TNF-α, IL-2, IL-12 and MIP-1α), while stimulating Th2 cytokine production (IL-5 and IL-10).
- Vitamin D inhibits transcription-factor activation (NF-κB and AP-1) and suppresses proinflammatory protein expression (iNOS, ICAM and VCAM).

Poly (ADP-ribose) polymerase

- Poly (ADP-ribose) polymerase (PARP) is a DNA-repair enzyme.
- PARP activation mediates cell death by both necrosis and apoptosis.
- PARP regulates gene transcription, protein expression and enzyme activity.
- PARP activation has been observed in a variety of disease states, including cardiovascular disease and inflammatory conditions.

Poly (ADP-ribose) polymerase & inflammation

- PARP activation leads to necrosis and release of cellular contents into the extracellular space, further triggering the inflammatory process.
- PARP inhibition protects against many inflammatory diseases.
- PARP inhibition suppresses transcription-factor (NF-κB and AP-1) activation affecting pronflammatory protein expression and production (IL-1, TNF-α, MIP-1α, iNOS, COX, ICAM and VCAM).

Vitamin D & poly (ADP-ribose) polymerase

- Vitamin D directly inhibits PARP.
- Vitamin D and PARP inhibitors share similarities in the diseases that they can protect against (rheumatoid arthritis, multiple sclerosis, Type I diabetes, colitis, cardiovascular disease and cancer) and their immunomodulatory effects (inhibition of Th1 immunity).
- Inhibition of PARP by 1,25$(OH)_2$D may mediate the immunomodulatory effects observed with both UVR exposure and vitamin D supplementation.

retinoids, thyroid hormone and vitamin D [109]. This interaction was proposed as a way of PARP influencing nuclear receptor signaling [109]. However, there remains the possibility that the reverse may be true – that interaction between nuclear receptors and PARP regulates PARP activity. In 2005 we demonstrated that gender differences in endotoxin-induced inflammation were related to PARP activation [110]; in this case, estrogen did not have an effect on PARP activity directly, but, when associated with estrogen receptor-α (ERα), could bind to the PARP protein. Therefore, when estrogen activates ERα and translocates to the nucleus, it forms a complex with PARP, preventing it from recognizing DNA strand breaks and hence becoming activated, protecting the cells [110]. Although it is yet to be investigated, a similar cellular action involving the VDR may exist. The VDR, together with the retinoic receptor following activation by vitamin D, may translocate to the nucleus, and similarly to ERα, form a complex with PARP and prevent its activation.

Conclusion

In summary, vitamin D has a wide range of effects on the function of various cells and tissues. One of these effects is the inhibition of the multifunctional nuclear enzyme PARP. The data overviewed in this paper are consistent with the view that vitamin D-mediated inhibition of PARP (Figure 1) may be one of the mechanisms by which

sunlight exposure (UVR) and vitamin D supplementation may exert immunomodulatory effects. Whether vitamin D also affects some of the other known actions of PARP (including regulation of cellular apoptosis/necrosis, DNA repair processes, cell proliferation and differentiation, vascular effects, effects on inflammatory cell migration, modulation of kinase pathways, and so on) remains to be elucidated in future studies. Inhibition of PARP through dietary vitamin D supplementation may prove effective in protecting against a wide variety of disease states.

Future perspective

Over the next 5–10 years we anticipate that there will be continued elucidation of the mechanisms involved in vitamin D-mediated immunomodulation, and the subsequent determination of the extent to which PARP inhibition regulates these effects. Additional mechanisms by which vitamins regulate cell function will continue to be identified, providing increased understanding in how our diet impacts our health status. The link between diet and disease susceptibility is already very strong, and the future development of specialized diets to reduce disease incidence in specific populations identified through genetics or global location will impact the epidemiology of inflammatory diseases. Finally, enzymes such as PARP are proving to be multifunctional cellular regulators, in addition to their primary functions as catalysts for chemical reactions. Revealing the multifunctional nature of individual enzymes in the future will allow for increased understanding of cellular regulation, in addition to providing new therapeutic targets for inflammatory diseases.

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Affiliations

- *Jon G Mabley*
School of Pharmacy and Biomolecular Sciences, University of Brighton, Cockcroft Building, Lewes Road, Brighton BN2 4GJ, UK
Tel.: +44 127 364 2055
Fax: +44 127 367 9333
j.g.mabley@brighton.ac.uk
- *Csaba Szabo*
Department of Surgery, University of Medicine and Dentistry of New Jersey, New Jersey Medical School, 185 South Orange Avenue, Newark, NJ 07103, USA
szabocsaba@aol.com