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Review Article

Recent advances on the roles of epidermal growth factor receptor in psoriasis

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Abstract: Epidermal growth factor receptor (EGFR) is a well-characterized receptor tyrosine kinase that involved in many vital activities in cell development, such as cellular homeostasis, proliferation, division, differentiation and apoptosis. Natural activation of EGFR and the concomitant downstream signaling pathways regulation are substantial to maintain normal cellular functions. In recent studies, EGFR was demonstrated to be a fundamental modulator in the control of skin inflammatory responses. Several dermatologic diseases including psoriasis are related to the anomalous activation of EGFR signaling. It has been proved that the expression and activity of EGFR and its endogenous ligands are overexpressed in the active epidermis lesions of psoriasis. Moreover, the remarkable therapeutic improvement of chronic psoriasis in cancer patients during the treatment of EGFR inhibitors or anti-EGFR monoclonal antibodies are also recorded, suggesting that the EGFR-mediated signaling may conduct a crucial role in the pathophysiology of psoriasis.

Keywords: EGFR, EGF, psoriasis, keratinocytes

Introduction

Epidermal growth factor receptor (EGFR) is one of the most complex and crucial signaling unit in physiology and pathology as a receptor tyrosine kinase. It is involved in many vital activities in cell development, such as cellular homeostasis, proliferation, division and differentiation, as well as apoptosis. It has also been demonstrated that EGFR conducts an essential role in the development of distinct organs such as brain, heart , bone, and several epithelia, including skin keratinocytes [1]. EGFR can be detected through the whole normal epidermis and is most prominently expressed in the proliferating basal cell layer [2]. Deregulation of EGFR signaling may lead to the development of psoriasis-like lesions, defects in wound healing, impaired hair follicles and tumorigenesis. A large variety of human dermatologic diseases are related to the anomalous activation of EGFR signaling, such as psoriasis, non-melanoma skin cancer and atopic dermatitis [3].

Psoriasis is an inflammatory immune-mediated, genetic disease that mainly affects the skin and is estimated to affect 0.09% to 5.1% of the population in the world [4]. Psoriasis vulgaris, also known as plaque psoriasis or chronic stationary psoriasis, occupies approximately 90% of psoriasis as the most common form. It is clinically manifested by raised, sharply demarcated, erythematous areas of inflamed skin covered with silvery-white lamellar scales [5]. This disease has significant negative effects on patients' health-related quality of life (HRQoL) and brings extremely heavy economic burden [6]. However, the pathogenesis of psoriasis is not fully understood. Several theories such as hyperproliferation of keratinocytes, genetic predisposition, environmental factors, innate immune and adaptive processes, have been emerged to demonstrate the pathological feature of psoriasis [7]. Recent studies have revealed that EGFR is overexpressed in psoriatic lesions [8] and may contribute to the pathogenesis of psoriasis.

In this review, we will introduce the activation and regulation of EGFR and discuss recent developments in the role of EGFR in psoriasis,

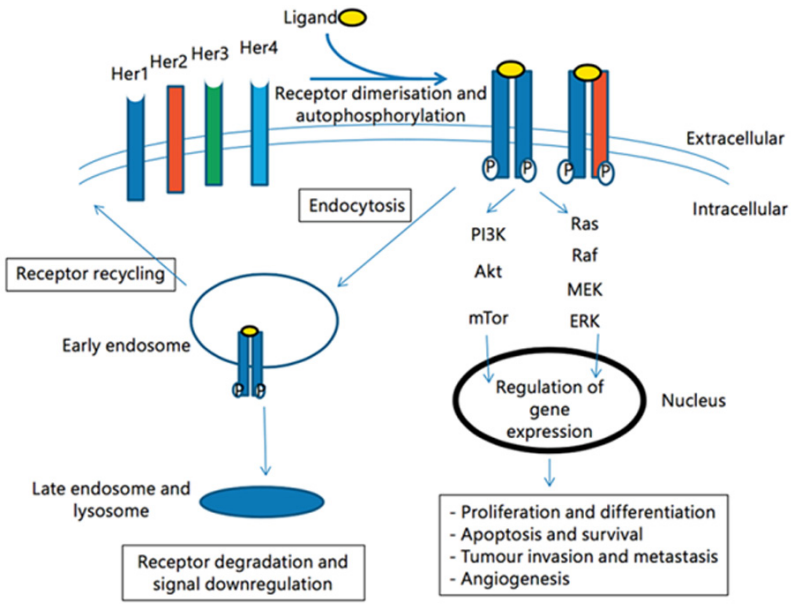

Figure 1. Diagram of the ErbB signaling and trafficking pathways. Binding of specific ligands to the extracellular domain of ErbB receptors leads to receptor dimerization, tyrosine kinase activation and autophosphorylation (P). Thus the activated ErbB receptors induce different downstream signaling pathways and play different roles in biology. Meanwhile, ErbB receptors are recycled through endosome trafficking or degraded by late endosome and lysosome.

providing insights into the management of EGFR-associated medication in psoriasis.

The EGFR/ligand system

The ErbB family of receptor tyrosine kinases

EGFR is a receptor tyrosine kinase (RTKs) that constitute one of the four members of the erythroblastic leukemia viral (v-erb-b) oncogene homolog (ErbB) receptors, which consist of ErbB1 (also known as EGFR), ErbB2 (also known as HER2/neu), ErbB3 (also known as HER3) and ErbB4 (also known as HER4). The former three isoforms are expressed in human skins [9]. All of the four members of the ErbB family share an analogous structure and have distinct roles in proliferation, differentiation, and development (**Figure 1** reproduced with permission from Actinic Keratosis) [10].

EGFR ligands and receptor activation

There are seven ligands has been proved to be involved in the acknowledged EGFR signaling activation: EGF, transforming growth factor-α (TGF-α), heparin-binding EGF-like growth factor (HB-EGF), amphiregulin (AREG), betacellulin (BTC), epiregulin (EREG), and epigen (EPGN), which are all rich in epidermal keratinocytes [11]. Binding of these ligands to the extracellular domain of ErbB receptors induces the formation of receptor homodimerisation (EGFR/EGFR) and hetero-dimerisation with other ErbB family members. These bindings further activate the intrinsic kinase domain of EGFR, leading to the phosphorylation of certain tyrosine residues in the cytoplasma, which are the binding sites for specific signal inducers, thereby lead to the subsequent activation of various downstream functional signaling pathways.

EGFR mediated signalings

The downstream pathways of EGFR signaling are extremely complicated and have been well described nowadays [12]. Ras-Raf-MEK-ERK pathway, also known as the mitogen-activated protein kinase (MAPK) cascade, is one of the most critical EGFR mediated signaling pathways. It is reported to be pivotal in the cell proliferation, differentiation, migration, apoptosis and tumorigenesis [13]. Other EGFR signaling downstream pathways include the PI3K/AKT pathway, STAT, the PLC-gamma/PKC, and NF-kB cascades etc [14]. Deregulation of these signaling pathways may lead to enhanced cellular invasiveness such as compromised apoptosis, induced cell proliferation, angiogenesis, tumor progression and metastasis [15].

EGFR endosomal trafficking

Endocytosis and delivery of endosomal cargos to lysosomes are crucial for the removal of many membrane-associated proteins including EGFR [16, 17]. Activated EGF receptors are internalized by endocytosis, and then are either trafficked through several endocytic compartments and packaged in lysosomes for proteolytic degradation or sorted into endosomes and recycled to the cell membrane recycled to the

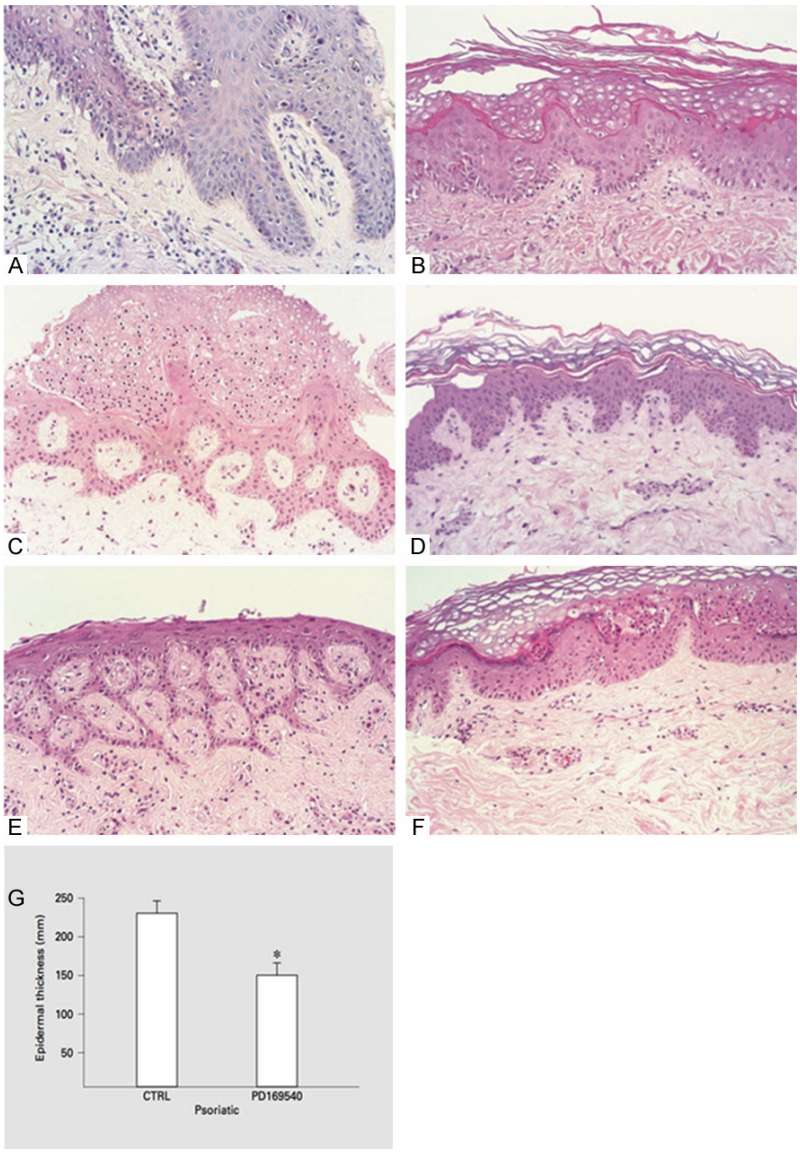

Figure 2. Effect of EGF receptor tyrosine kinase antagonist PD169540 on the histologic features of psoriatic lesion in skin organ culture. A, C, E: Psoriatic lesional skin from three patients without EGF-RTK antagonist. B, D, F: Psoriatic lesional skin treated with 1 μM EGF-RTK antagonist PD169540. HE. X89. G: Quantification of epidermal thickness. The thickness value of epidermal for antagonist-treated skin was significantly reduced compared to the untreated control ($P<0.05$).

cell surface [18-20]. With the maturation of endosomes, EGFR is sorted into the multivesicular endosomes/bodies (MVBs) [21], which merge with lysosomes and lead to the degradation of EGFR. Therefore, endosomal trafficking of EGFR is essential for establishing the intensity and duration of EGFR signaling [22, 23].

EGFR in skin inflammation

In recent studies, EGFR is demonstrated to be critical in the control of skin inflammatory responses [24, 25]. The most common examples are that cancer patients receiving EGFR inhibitors usually suffer from cutaneous inflammatory toxicities, such as flushing, an acne-like rash, and folliculitis. The development and severity of these side effects can be strong clinical predictors for the efficacy of EGFR inhibitors treatment [26]. It has been proved that dendritic cells, macrophages, granulocytes, mast cells, and T cells are involved in the early inflammatory infiltrate of the skin rash caused by EGFR inhibitors [2]. And these inflammatory cells are recruited by proinflammatory mediators including CCL2, CCL5, and CXCL10, which can be induced by cytokines such as tumor necrosis factor-α (TNF-α) when EGFR signaling is inhibited [2]. Furthermore, EGFR inhibitors can also impair the formation of antimicrobial peptides and skin barrier proteins, leading to an increased permeability of skin and a defect in antimicrobial defense. Patients treated with EGFR inhibitors are at a great risk of developing bacterial skin infections [27]. In addition, one study showed that mouse lacking epidermal EGFR can get a chemokine-driven skin inflammation, hair follicle degeneration, compromised host defense, impaired skin barrier function and early death [24].

Roles of EGFR in psoriasis

Psoriasis is a common chronic immune-mediated inflammatory disease, which is characterized by the loss of normal cellular homeostasis, leading to the hyperproliferation of keratinocytes, altered differentiation with parakeratosis, and inflammatory infiltrate with increased

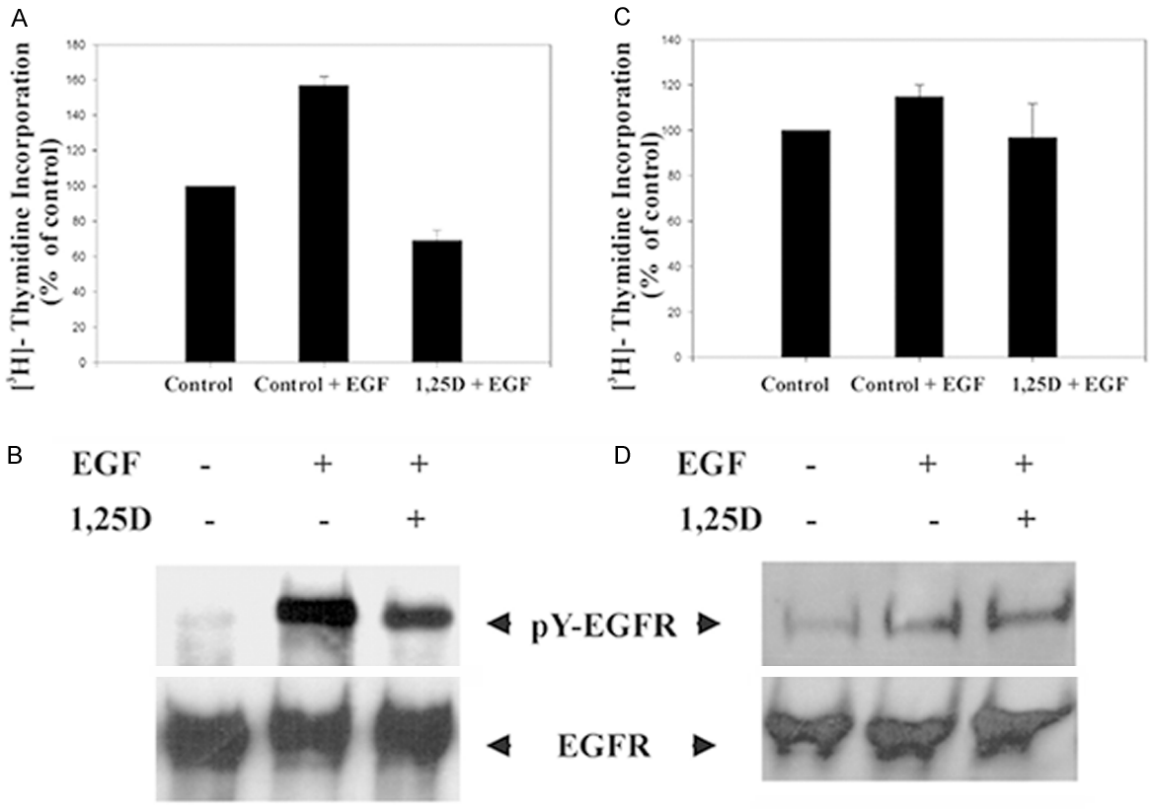

Figure 3. $1,25(OH)_2D_3$ inhibits cell proliferation and the activation of EGFR in EGFR-overexpressing cells. NR6 (A) and HeLa (C) cells were incubated in the presence or absence of 100 nM $1,25(OH)_2D_3$ for 48 h with or without 17 nM EGF for the final 24 h. Cell proliferation was measured by [^{3}H]thymidine incorporation into DNA. NR6 (B) and HeLa (D) control cells or cells treated with $1,25(OH)_2D_3$ were incubated with or without 17 nM EGF for 20 min at 37°C. Cellular extracts immunoprecipitated with anti-EGFR antibody and analyzed by Western blot for total EGFR and tyrosine-phosphorylated EGFR.

secretion of proinflammatory cytokines in the epidermis [28].

EGFR and its ligands are up-regulated in psoriatic lesions

Some recent studies proved that the expression and activity of EGFR and its ligands (TGF-α, Amphiregulin and HB-EGF) are overexpressed in the epidermis of active psoriatic lesions [8, 29-32], as a result of the preservation of the receptors in the parakeratotic stratum corneum, suggesting that the EGFR-mediated hyperstimulation of keratinocyte could impact the development of psoriatic lesions [8, 33]. Varani J el. exposed non-psoriatic skin to EGF in organ culture and it developed the histological features mimic the skin of psoriatic lesions. After being cultured in the presence of an antibody of epidermal growth factor receptor for several days, the psoriatic tissue was partially alleviated, indicating that the growth factors acting through the EGFR are critical in maintaining the psoriatic phenotype in organ culture [34]. Another study revealed that the psoriatic phenotype in organ-cultured skin was improved by inhibiting the EGFR tyrosine kinase, but no significant effect on the non-psoriatic skin (**Figure 2** reproduced with permission from Skin Pharmacol Physiol) [35]. Moreover, Flisiak el. found that serum EGF levels were increased and serum EGFR levels were decreased in psoriasis patients compared with controls, and both had a correlation with disease severity [36].

CCL27, key chemokines implicated in psoriasis is up-regulated when treated with EGFR inhibitors

CCL27, also known as cutaneous T-cell attracting chemokine (CTACK), is associated with homing of memory T cells to the skin, and plays an important role in T cell-mediated inflamma-

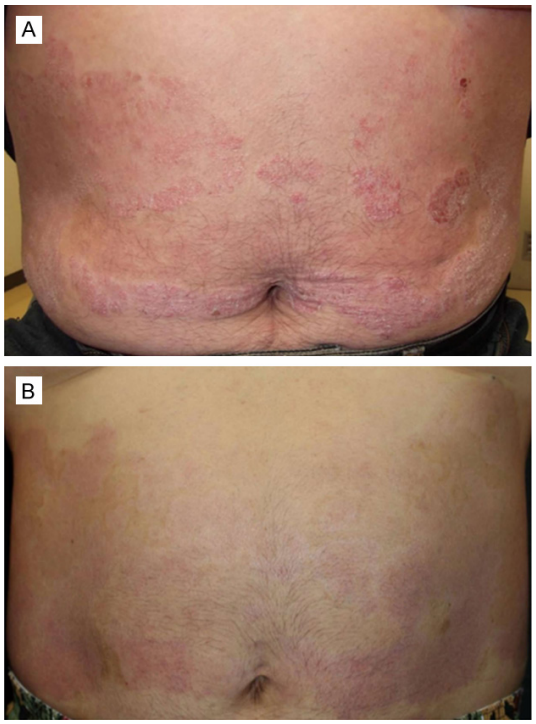

Figure 4. Improvement of psoriasis vulgaris in cancer patients after the treatment of anti-EGFR monoclonal antibody cetuximab. A: Manifestation of the raised, clearly demarcated, erythematous plaques covered with silvery-white lamellar scales before the treatment of cetuximab; B: Remarkably improvement of psoriasis skin lesions after initiation of cetuximab.

tion of the skin [37]. It has been shown that CCL27 is correlated with psoriasis in a mutually antagonistic way, and serum CCL27 concentration relates to disease severity [38]. Lichtenberger BM el. found an induction of CCL27 in the sera of patients treated with EGFR inhibitors, which was much stronger than the CCL27 levels observed in sera of patients suffering from psoriasis vulgaris [24]. Another study proposed that IFN-γ and TNF-α active the phosphorylation of EGFR and then downregulate CCL27 expression, which can induce inflammation characteristic for long-lasting psoriasis plaques in the late stage of the disease [39].

1,25(OH)$_2$D$_3$ acts through EGFR signaling pathway to treat psoriasis

As a drug that commonly used for the treatment of psoriasis, 1,25(OH)$_2$D$_3$ is highly effective in arresting keratinocyte growth and the progression of psoriatic lesions. Some recent works showed that 1,25(OH)$_2$D$_3$ inhibits TGF-α and EGF-induced cell proliferation, changes the localization of TGF-α and EGFR, and suppress ligand-dependent EGFR and ERK1/2 activation, suggesting that 1,25(OH)$_2$D$_3$ acts through the TGF-α/EGFR signaling pathway to suppress cell growth in psoriasis (**Figure 3** reproduced with permission from J Biol Chem) [40, 41].

EGFR inhibitors improve psoriatic lesions

Recently, some of the EGFR kinase-blocking agents have been reported to display an antiproliferative function in psoriatic lesions [42]. Clinically, various drugs target EGFR are applied for cancer chemotherapy, including the small molecule tyrosine kinase inhibitors erlotinib, gefitinib, and lapatinib, and monoclonal antibodies that target the extracellular domain, such as cetuximab and pertuzumab. Several studies have recorded the remarkable therapeutic improvement of chronic psoriasis in cancer patients during the treatment of EGFR inhibitors erlotinib [43-45], lapatinib [46], and the anti-EGFR monoclonal antibody panitumumab [47] and cetuximub (**Figure 4** reproduced with permission from World J Gastroenterol) [47-50] (**Table 1**). Besides, another study revealed that elevated expression of the pro-inflammatory cytokine granulocyte/macrophage-colony stimulating factor (GM-CSF) is associated with high epidermal levels of EGFR activation in lesional skin of psoriatic patients [51]. Remission of the disease by the inhibition of EGFR activity may be the result of reduced level of keratinocyte-derived GM-CSF. Intriguingly, Marinello el. reported a paradoxical case of a pustular psoriasiform drug eruption induced by EGFR inhibitor cetuximab in a colorectal cancer patient, as the result of the disequilibrium of downstream molecular signaling pathways owing to the EGFR signal blockade [52]. All of these facts suggest that the EGFR-mediated signaling may be a significant regulator in the pathophysiology of the disease. Further researches are needed to better elucidate the comprehensive function of EGFR in psoriasis in the further.

Conclusion

EGFR is widely expressed in skin tissues and is a major modulator of cellular proliferation, differentiation, migration and inflammation in the epidermis [53]. The skin homeostasis requires natural EGFR binding with diverse ligands and subsequent activation and regulation, as well

Table 1. EGFR inhibitors application in cancer patients relieves psoriasis

EGFR inhibitor	Cancer	Other received drug therapy	References
Erlotinib	Non-small cell lung cancer	Unknown	[44]
Erlotinib	Squamous lung cancer	Unknown	[44]
Erlotinib	Lung adenocarcinoma	Platinum, antihistamine therapy	[45]
Lapatinib	Metastatic kidney tumour	Interleukin-2, progesterone	[46]
Cetuximab	Colon cancer	Capecitabine, bevacizumab, IRIS	[47]
Panitumumab	Colon cancer	Capecitabine, bevacizumab, IRIS	[47]
Cetuximab	Colorectal cancer	5-FU, LV, capecitabine, irinotecan, oxaliplatin	[48]
Cetuximab	Metastatic colon cancer	Irinotecan, 1-folinic acid, 5-FU	[49]

5-FU = 5-fluorouracil; LV = leucovorin.

as triggering downstream pathways that correlated with various cellular functions and biological behaviors. The alterations in EGFR metabolism and downstream signaling coordination might be implicated in the etiopathogenesis of different types of skin disorders, for instance, psoriasis.

Psoriasis is a chronic inflammatory skin disease with multi-pathogenesis that typically involves in increased keratinocyte proliferation, vascular hyperplasia, fibroblast activation as well as inflammatory cell infiltration into psoriatic lesions, which all lead to the changes of essential cytokine production [54]. It is widely reported EGF and EGFR expression level is significantly altered in psoriasis [8, 36]. Moreover, patients treated with EGFR inhibitors have been frequently found to be diagnosed with skin toxicities, which resulted from immune cells dysfunction and chemokines deregulation in epidermis, and may serve as a valuable predictor for therapeutic efficacy [24]. These findings indicate that the aberrant expression of EGFR and downstream pathway activation may contribute to the pathogenesis of psoriasis, and the application of EGFR inhibitors might be potentially effective to prevent the genesis and development of psoriasis [55].

To conclusion, EGFR is a vital regulator in the epidermis equilibrium and its overexpression is associated with psoriatic lesions. The inhibition of EGFR expression and activation may be a potent strategy to counteract the progression of psoriasis. However, a comprehensive understanding of the regulation network for EGFR and its ligands, as well as downstream signaling pathways implicated in psoriasis are still not fulfilled. Further studies are required to reveal the mechanism of specific EGFR function in psoriasis.

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Disclosure of conflict of interest

None.

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