INNATE LYMPHOID CELLS: ROLES IN TUMOUR GENESIS AND PROGRESSION

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UROĐENE LIMFOIDNE ĆELIJE- ULOGA U GENEZI I RASTU TUMORA

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ABSTRACT

Innate lymphoid cells (ILCs) represent the most recently identified members of the innate immune system. These cells play important roles in inflammation, tissue remodelling and metabolic disease. ILCs can be subdivided into three major groups according to their cytokine production. The role of ILCs in tumourigenesis and tumour progression is not completely clarified. In this review, we discuss whether and how ILCs are involved in tumour genesis, growth and metastasis.

Keywords: *Innate lymphoid cells, tumour, progression, antitumor immunity*

SAŽETAK

Urođene limfoidne ćelije (engl. Innate lymphoid cells- ILCs) predstavljaju populaciju nedavno opisanih ćelija urođene imunosti. Ove ćelije igraju značajnu ulogu u zapaljenju, obnavljanju tkiva i metaboličkim poremećajima. U zavisnosti od produkcije citokina, ILCs se mogu podeliti u tri glavne subpopulacije. Uloga ILCs u tumorogenezi i progresiji bolesti nije u potpunosti razjašnjena. U ovom preglednom članku, mi razmatramo da li i kako ILCs utiču na genezu, rast i metastaziranje tumora.

Ključne reči: *Urođene limfoidne ćelije, tumor, progresija, antitumorska imunost*

INNATE LYMPHOID CELLS

The innate immune response is important in combating various microbes during the early phases of infection. Innate lymphoid cells (ILCs) represent the most recently identified constituents of the innate immune system by playing a role in inflammation, tissue remodelling and metabolic disease (1). ILCs lack the known immune cell lineage markers. Unlike T and B lymphocytes, ILCs do not have antigen receptors and memory functions (2). ILCs are localized in intestinal and lung mucosae as well as the skin and are capable of rapidly switching on responses to pathogens, even upon first exposure (1). These cells can be subdivided into three major groups according to their cytokine production (Fig 1; 3-4). The ILC2 group represents the innate equivalent of Th2 cells. This group only includes ILC2 cells (e.g., nuocytes, natural helper cells, innate helper cells, and multipotent progenitor cells) that secrete IL-5 and IL-13 in response to IL-25, IL-33 and thymic stromal lymphopoietin (TSLP), and they mediate innate responses during helminth infections and allergies (1-2). The ILC1 group is composed of ILC1 cells and natural killer (NK) cells. They represent the innate equivalent of adaptive Th1 and cytotoxic T cells, respectively. While NK cells play well-known roles in antiviral and antitumour immunity, several additional ILC1s have recently been identified that produce IFN-γ. The ILC3 group includes ILC3 cells and lymphoid tissue inducer (LTi) cells (1, 5). These cells mainly secrete IL-17 and IL-22 in response to IL-23 and IL-1b, and they represent the innate equivalents of Th17 and Th22 cells, respectively. The development and differentiation as well as effector functions of the ILCs are dependent upon the transcription factor, GATA3 (1, 6).

The role of ILCs in inflammatory immune responses, tissue remodelling and metabolic disease are well documented (Fig 1; 1, 2, 7). Recent studies described the involvement of ILCs in tumour growth and progression (8-11). In this paper, we summarize the role of ILCs in tumour genesis and anti-tumour immunity modulation.

THE HISTORY OF INNATE LYMPHOID CELLS

Natural killer (NK) cells were the first discovered ILCs. Five years ago, a new type of innate lymphoid cells was described in fat-associated lymphoid clusters (FALCs). These cells did

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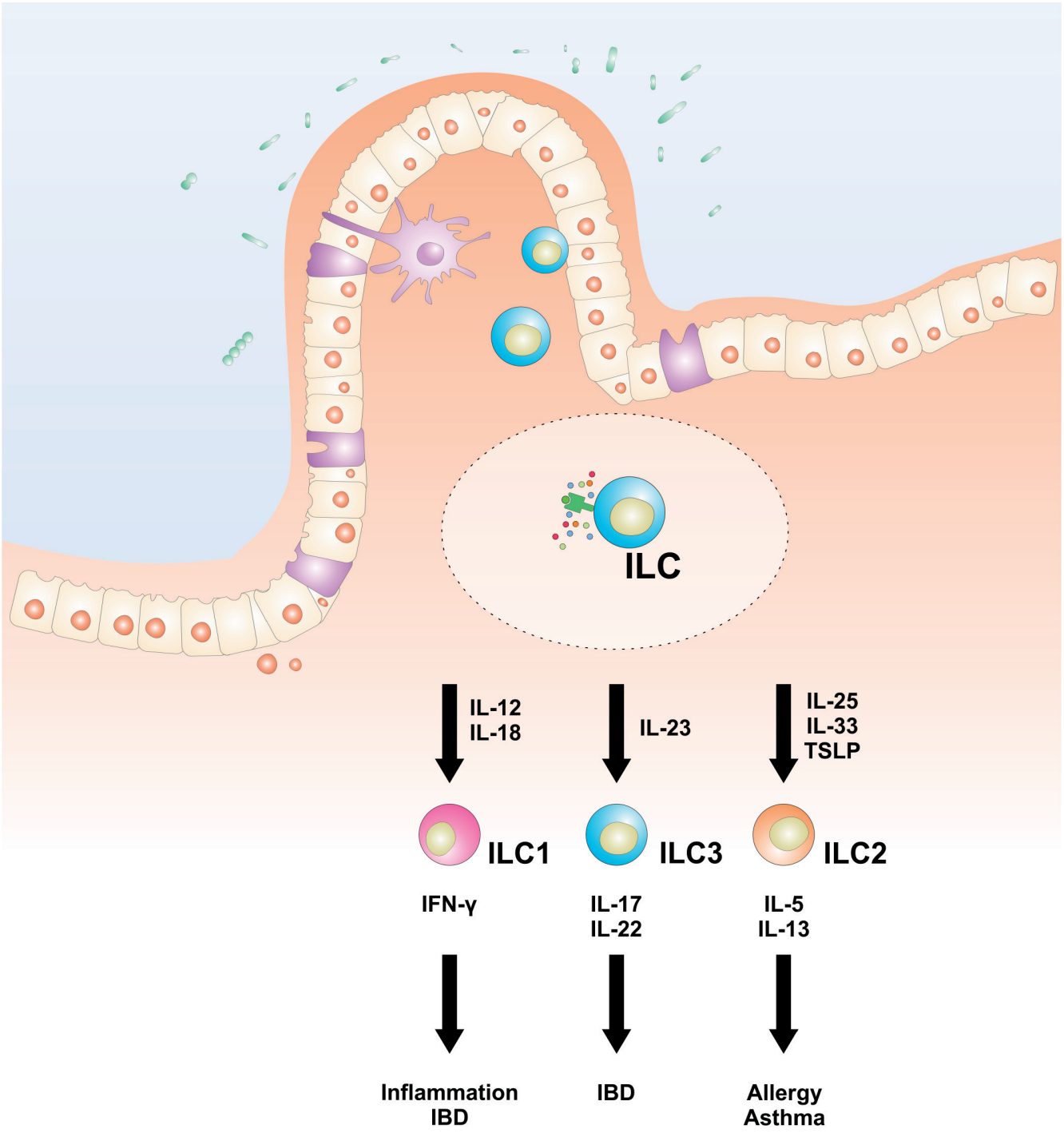

Figure 1. Innate lymphoid cell classifications. The classification of innate lymphoid cells (ILCs) is based on functional criteria. ILC1s are defined by their capability to produce interferon-γ (IFNγ). ILC2s produce type 2 cytokines, interleukin-5 (IL-5) and IL-13. ILC3s are capable of producing the type 17 cytokines IL-17 and IL-22. Different subsets of ILCs cells play various roles in disease immuno-pathogenesis and subsequent tissue destruction and systemic manifestations.

not express lineage (Lin) markers but expressed c-Kit, Sca-1 (also known as Ly6a) and ST2 (12). The authors named them natural helper cells (NHCs). NHCs were shown to proliferate in response to IL-2 and to produce large amounts of type 2 cytokines such as IL-5 and IL-13 in response to IL-33 stimulation and also to require IL-7 for survival (12). NHCs regulate B-cell antibody production and self-renewal of B1 cells. The authors concluded that the described FALC Lin$^-$ c-Kit$^+$ Sca-1$^+$ cells (NHCs) acted like Th2-type innate lymphocytes (12). Novel innate lymphocytes, termed multipotent progenitor (MMP) cells, were discovered at a same time (13). IL-25 (also known as IL-17E) promotes the accumulation of Lin$^-$ Sca-1$^+$ c-Kit^{int} MMP cells in gut-associated lymphoid tissue with subsequent type 2 cytokine production (13). In the same year, this second group of investigators identified a population of lineage negative IL-13 producing cells (14). They named them "nuocytes" due to their IL-13 production (nu is the 13th letter of the Greek alphabet). These cells did not express Lin markers but expressed ICOS, ST2, IL17BR and IL17Rα (14). Nuocytes play a critical role in inducing helminth expulsion. These cells expand rapidly in response to IL-25 and IL-33 (type 2 inducing cytokines) and in response to infection of the helminth, *Nippostronglylus brasiliensis*. Nuocytes secrete high IL-5 and IL-13 levels and present highly specialized type 2 regulatory cells (14). Three independent research groups defined innate lymphoid cells, termed multipotent progenitor (MMP) cells, natural helper cells and nuocytes in the gut-associated mucosa tissues, in the same year (12-14). Whether these cell types exist in organs other than the digestive system was unknown. At that time, it was already known that intranasal administration of the type 2-inducing cytokines, IL-25 and IL-33, induced eosinophilia in the lungs of mice lacking T and B lymphocytes, indicating that another cell population was capable of facilitating localized inflammation (15). Chang et al. reported the presence of Lin$^-$ c-Kit$^+$ Sca-1$^+$ ST2$^+$ cells in the lungs and their contribution to the development of airway hyper-reactivity via IL-33 signalling (16). In this study, H3N1 influenza infection induced airway hyper-reactivity, which is a cardinal feature of asthma, through the accumulation and activation of innate lymphoid cells. These cells produced large amounts of IL-5 and IL-13, which facilitate the genesis and progression of airway hyper-reactivity and intensive mucus secretion in the airways (16). Another research group described innate lymphocytes, termed lung natural helper (LNH) cells, as a T cell-independent source of type 2 cytokines (17). The cells were defined as Lin$^-$ Sca-1$^+$ c-Kit$^{+/lo}$ CD25$^+$ CD127$^+$ cells. After stimulation with IL-33 and IL-2, IL-7 or TSLP, the LNH cells produced IL-5 and IL-13 (17). Innate lymphoid cells in the lungs were capable of rapidly responding to lung epithelium-derived cytokines. Further, they can be divided into two distinct populations: NK cells and cytokine producing ILCs (17). Barthemes et al. described the IL-33 responsive ILCs that reside in the lungs (18). These lung lymphoid cells were Lin$^-$ c-Kit$^-$ Sca-1$^+$ CD44$^+$ CD25$^+$ Thy1.2$^+$ IL-7Rα$^+$ ICOS$^+$ and produced large quantities of IL-5 and IL-13 after exposure to the fungal allergen, *Alternaria alternata* (18). The authors suggested that allergic airway inflammation can develop independently of adaptive immunity, and lung Lin$^-$ CD44^{hi} CD25$^+$ cells were sufficient to induce airway inflammation (18). An important pathogenic role of novel ILCs was confirmed by the identification and expansion of these cells in various allergy and parasitic inflammation models (18-21). ILCs are important producers of IL-9 during airway inflammation (14, 22). It has now been shown that Lin$^-$ ST2$^+$ cells are the main source of IL-9. IL-33 was shown to induce the accumulation of ILCs that produce IL-9 (22).

Additionally, ILCs play an important role in tissue remodelling. It was shown that, during influenza virus-induced airway inflammation, ILCs produce the epidermal growth factor-related cytokine, amphiregulin, which further regulates epithelial cell repair (23).

Common traits for all types of the described innate lymphoid cells are that they are systemically dispersed and expanded in response to IL-33 and/or IL-25, *in vivo*, express similar surface markers and produce large quantities of IL-5 and IL-13 after activation (24). This finding indicates that these populations might be closely related. All of these cells have been classified into the ILC2 group.

ILC1s are defined by the production of IFNγ and the inability to produce type 2/17 cytokines (1, 2). The prototypical member of this group is the NK cell. First discovered in 1975, natural killer (NK) cells were the first discovered ILCs (25). Unlike T and B lymphocytes, these innate lymphocytes do not express antigen receptors but rapidly exhibit cytotoxic activities against virus-infected and tumour cells and produce various cytokines (1, 2). The origins and roles of NK cells in anti-viral and anti-tumour immunity are well established and they will not be discussed here. NK cells not only display cytotoxic activity, but they are also able to produce large quantities of IFN-γ following activation. Recent studies have identified another ILC1 subset that produces IFN-γ (2, 26, 27). These cells do not secrete type 2/17 cyto-

Table 1. Innate lymphoid cells in tumour genesis and progression

ILC2s	Eosinophil accumulation and antitumour immunity via IL-5 (11)
	MDSCs and Treg accumulation and immunosuppression via IL-13 (8)
	Carcinogenesis via IL-13 (51,52)
ILC3s (IL-17$^+$)	Facilitate tumourigenesis, angiogenesis and metastasis (55)
ILC3s (IL-22$^+$)	Stimulate pro- and anti-tumour mechanisms (59)
ILC1s (NK)	Antitumour cytotoxicity and facilitate potent antitumour immunity (62-66)

kines and represented a population that is distinct from NK cells (2, 26, 27). The development of NK cells is dependent upon T-bet expression, and they occur independently of GATA3, while the development of ILC1s is dependent upon both GATA3 and T-bet expression (4). ILC1 cells express high T-bet levels and low RORγt levels (27). These $CD117^-$ cells express IL-7Ra and CXCR3 and secrete IFN-γ, TNF-α, CCL3, and CCL4 in response to activation via IL-12, IL-15 and IL-18, and they play role in immune defence to Salmonella spp. infections and in Crohn's disease immunopathogenesis (1, 2, 27-29).

A recent study described various ILC3 subsets in intestinal tissues (1, 5, 30-33). The ILC3 group includes ILC3 cells and lymphoid tissue inducer (LTi) cells (1, 5). One of the ILC3 subsets that was described in the tonsils, Peyer's patches, appendix and colon lamina propria consists of cells that expresses the NK cell receptor, NKp44/NKp46, and CCR6 and secretes IL-22 but not IL-17 upon IL-23 stimulation (30-32). Another ILC3 subset was discovered in disease affected tissue of Crohn's disease patients and secretes IL-17 and IFN-γ (33). Foetal mesenteric lymph nodes harbour ILC3s that secrete IL-17 and IL-22 (34). LTi cells, which are mediators of innate immunity, can be activated via an IL-23-dependent manner and represent the dominant source of IL-22 during early infections (36). ILC3s mainly secrete IL-17 and IL-22 in response to IL-23 and IL-1b, and represent the innate equivalents of Th17 and Th22 cells (30-35). IL-22 triggers antimicrobial peptide release and promotes epithelial cell proliferation, thereby preserving epithelial barrier integrity (1, 2, 5, 30-35). IL-17 elicits neutrophil recruitment. A recent study found that ILC3s, in particular LTi cells, express MHC class II molecules and present antigen to $CD4^+$ T cells, indicating an impact of ILC3s on adaptive immune responses (37). However, interactions with T lymphocytes did not lead to activation and subsequent proliferation, but these interactions led to tolerance of presented antigens (37). Cella et al. revealed that $NKp44^+$ ILC3s produce BAFF (B-cell activating factor) and promote B-cell activation and survival within mucosal tissues (30, 32).

THE ROLE IF ILCS IN TUMOUR GROWTH AND PROGRESSION

The role of ILC2s in tumour growth and progression was established in a few tumour models (Table 1). A recent report showed that IL-33 mediated an increased level of IL-5-producing ILCs that further regulated the antitumour activity of eosinophils in a lung tumour metastasis model (11). In this study, the authors used a lung metastatic melanoma cell line and observed an accumulation of innate IL-5-producing cells that regulated eosinophil influx into the lung. The innate IL-5-producing cells were similar to the natural helper cells, nuocytes and innate type 2 helper cells, and the majority of which were lineage negative and expressed Sca-1, Thy1.2, CD25, CD27, CD44, CD69, IL-7Ra and ST2, which is a subunit of IL-33R (11). Further, they showed responsiveness of ILCs to IL-25 and IL-33, indicating that these IL-5-producing cells belong to the ILC2 class of cells. After induction of a lung metastatic melanoma model, the authors found that exogenous IL-25 and IL-33 mediated infiltration of eosinophils into the lung via IL-5. Specifically, IL-25 and IL-33 induced accumulation of the innate IL-5-producing ILC2s, which in turn recruited eosinophils into the lung. Antitumour immunity is mediated by the innate and adaptive immune system (38, 39, 40, 41, 42). Polarization of antitumour immune response influences tumour growth in a dual manner. Polarization towards the type 1 response preferentially activates cellular immunity (by producing IFN-γ and IL-2), while the type 2 immune response suppresses cellular immunity by eliciting humoral immunity (via IL-4, IL-5 IL-10, and IL-13 production) (40, 43- 45). The type 1-mediated antitumour immune response is followed by potent stimulation of T-cell cytotoxic activity (39, 40, 41, 46). On the contrary, type 2 polarization results in the production of growth factors and cytokines that support tumour growth and metastasis (43). Although type 2 cytokines downregulate antitumour immunity, they can promote the recruitment of tumouricidal eosinophils and macrophages into the tumour microenvironment (40, 41, 43, 44). In the present study, Ikutani et al. concluded that ILC2s facilitate the accumulation of tumouricidal eosinophils in the lung and may play an important role in tumour surveillance (11). However, eosinophils possess both pro- and anti-tumour activities that are dependent on the tumour microenvironment and type (47, 48). The role of ILC2s in tumour growth needs to be further clarified.

Our initial work on this subject was based on a highly malignant and poorly immunogenic murine tumour model, which shares many characteristics with naturally occurring human breast cancer (8). In this study, we aimed to investigate the effects of exogenously administered IL-33 on tumour appearance and progression and on the mechanisms of anti-tumour immunity. We found that IL-33 enhanced mammary carcinoma growth and lung and liver metastasis by facilitating the expansion of immune suppressor cells within the tumours and by diminishing innate anti-tumour immunity (8). IL-33 administration expanded IL-13 producing innate lymphoid cells within the mammary tumour. These tumour infiltrating lymphoid cells were $CD45^+$ Lin^- $Sca\text{-}1^+$ $CD44^+$ $CD25^+$ $ST2^+$ and produced IL-5 and IL-13 in response to IL-33 and were IL-4, IL-10 and IFN-γ negative, indicating that they had an ILC2 phenotype (8). IL-33 increased the frequencies of IL-5 and IL-13 expressing ILCs and circulating levels of IL-13 in tumour-bearing hosts (8). ILC2s have been shown to facilitate Type 2 immune responses while preventing Type 1-mediated immunity (11, 12, 14, 17, 49); however, their roles in cancer progression are not well defined. We assumed that ILCs directly affect myeloid-derived suppressor cell (MDSC) activity via IL-13. MDSCs are usually recruited to tumour sites from peripheral lymphoid organs where they promote the $CD4^+Foxp3^+$ Treg generation (IJC 33) and exert immunosuppressive effects via TGF-b production. It is well known that MDSCs require the presence of IL-13 for

their activity, e.g., arginase and nitric oxide synthase II expression (50). In line with our conclusion, we also demonstrated IL-33 mediated an increase of $CD11b^+$ $CD11c^-$ $Gr\text{-}1^+$ MDSCs within mammary tumours (8). These MDSCs expressed IL-13α1 receptors and produced TGF-β (8). Our findings revealed a novel role for IL-33 in the mechanisms of breast cancer immune escape via the ILC2s/IL-13/MDSCs/ TGF-β/Tregs axis (8).

In another study, intra-biliary injection of IL-33 into mice with active Akt and Hippo pathways facilitated cholangiocarcinoma development, indicating a role of IL-33 in cholangiocyte proliferation, biliary repair, and carcinogenesis via the ILC2s/IL-13 axis (51, 52).

The role of ILC3s in tumour growth and progression was also described (Table 1). $ROR\gamma t^+$ ILC3s are a main source of IL-17 and IL-22 (second to Th17 cells in terms of production) (53). Studies have shown that $ROR\gamma t^+$ ILC3s accumulate in the intestine of inflammatory bowel disease (IBD) patients and are a crucial IBD pathogenic factor (33, 53). In chronic gastrointestinal infection or acute stimulation with chemical carcinogens, IL-17-producing $IL\text{-}23R^+$ ILC3s induce gut tumourigenesis through the IL-23/IL-17 signalling pathway, which promotes angiogenesis and tumour metastasis (54, 55). Some experiments suggested that IL-22 producing ILC3s promote inflammation in active intestinal diseases (33, 56-58). IL-22 may promote pro- and anti-tumour mechanisms depending on the tissue microenvironment and tumour characteristics. Thus, in pathogen-induced cancers, IL-22 inhibits tumour growth by promoting the elimination of viral or bacterial infections and termination of inflammation. In contrast, IL-22 may facilitates angiogenesis and promotes cancer growth (59). Studies have shown that IL-22 together with other factors contributes to tumour formation (60, 61).

It has been known for decades that NK cells provide protection against viruses and tumour cells. The role of NK cells in immune surveillance is well established (62-66). NK cell activity is variable during tumour progression and is related to clinical stages and disease outcome (65-70). During the cytotoxic killing of tumour cells, NK cells and $CD8^+$ T cells rapidly release granules that contain perforin and granzymes into immunological synapses, thereby inducing target cell death (71). NK cell activity is the major mechanism of innate immunity against tumours (42). NK cells lyse tumour cells without prior sensitization and represent the first line of defence against tumours and cancer metastasis (42).

Recent studies have achieved significant progress towards defining subpopulations of ILCs. ILC1s, ILC2s and ILC3s are now emerging as important cell populations that regulate tissue homeostasis and inflammation. Several studies have described the effects of ILCs on the genesis, growth and progression of tumours and the modulation of antitumour immune responses. However, much of the current knowledge regarding ILCs is based on experimental models and still requires confirmation in humans. Extensive clinical investigations are still needed to clarify the intrinsic roles of ILCs in response to tumours.

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CONFLICT OF INTEREST

The authors declare no financial or commercial conflicts of interest.

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