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Role of BCR and FNBP1 Proteins in Phagocytosis as a Model of Membrane Rearrangements with Chronic Myelogenous Leukemia

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Abstract—Chronic myelogenous leukemia (CML) is a myeloproliferative neoplasm resulting from the emergence of abnormal hematopoietic stem cells carrying a Bcr-Abl oncoprotein as a result of a reciprocal translocation between the chromosomes 9 and 22. The main elements of the disease's pathogenesis are caused by both increased tyrosine kinase activity of the Abl protein and the role of a Bcr part of the hybrid protein. The presence of PH domain in the Bcr determines its interaction with PI(3)P of the phagosomal membrane. We demonstrated that this interaction is accompanied by a colocalization of the Bcr with the FNBPI protein in the phagosomes of J774 macrophage cells. A model of the effect of the Bcr-Abl oncoprotein on the formation of the ROS excess with CML due to uncontrolled expression of phagosomal NADP oxidase is presented.

Keywords: chronic myelogenous leukemia, Bcr-Abl, FNBP1, phagosome, NADP oxidase

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INTRODUCTION

Chronic myelogenous leukemia is a myeloproliferative neoplasm resulting from the emergence of abnormal hematopoietic stem cells carrying a Bcr-Abl oncoprotein as a result of a reciprocal translocation between the chromosomes 9 and 22 (Flis and Chojnacki, 2019; Hamad, 2021; Liu et al., 2023). The hybrid Bcr-Abl protein has a constitutive tyrosine kinase activity due to the Abl part, which leads to abnormal cell signal transduction and blast transformation (Zhang and Li, 2013; Liu et al., 2023). Depending on the breakpoint in the *BCR* gene, different forms of Bcr-Abl are expressed (particularly, p190, p210, and p230) that, despite the same tyrosine kinase activity, are associated with different types of the disease (acute lymphoblastic leukemia, chronic myelogenous leukemia, and relatively benign chronic neutrophilic leukemia, respectively) (Kang et al., 2016; Peiris et al., 2019; Huma and Suhaib, 2021). Different forms of Bcr-Abl are characterized by unexpectedly large differences in the interactome and tyrosine phosphoproteome, although the presence or absence of DH and PH domains of the Bcr part is the only structural difference between them, while the Abl part remains constant (Cutler et al., 2017; Reckel et al., 2017a; Antonenko and Telegeev, 2020a). The PH domain interacts with phosphoinositides typical for lipid membranes and the Golgi complex and is involved in the cell signaling and formation of endocytosis vesicles (Lenoir et al., 2015; Antonenko et al., 2016; Gurianov et al., 2016; Reckel et al., 2017b).

According to the preliminary results of mass spectrometric analysis, we identified 23 proteins that are potential candidates for the interaction with the PH domain of the Bcr-Abl oncoprotein (Miroshnychenko et al., 2010). Among them is formin-binding protein 1 (FNBP1), also known as formin-binding protein 17 (FBP17). FNBP1 was for the first time identified as a protein that binds to a proline-rich region of formin (Aspenstrom, 2010; Wang et al., 2022). FNBP1 belongs to a F-Bar/EFC family of proteins widely expressed in eukaryotic cells. FNBPI is involved in the rearrangement of the membrane bound cytoskeleton by actin polymerization, which is an important condition for the cell signaling and receptor-mediated endocytosis (Yoon et al., 2021). Due to a complex domain organization, where the N-terminal Fer/CIP4 homologous domain, helical domain, and proline-rich motif provide tubular invagination of the cell membrane, FNBP1 regulates the membrane curvature and is a sensor protein of its tension (Kamioka et al., 2004; Yoon et al., 2021). FNBP1-mediated activation of a N-WASP-WIP protein complex affects the formation of podosomes and phagocytic cups and increases the plasma membrane tension (Tsujita et al., 2015; Wang et al., 2022). The attraction of dynamin-2 to the plasma membrane with the involvement of the FNBP1 protein SH3 domain provides the formation of invadopodia (Yamamoto et al., 2011). Thus, the

FNBP1 is one of the key factors regulating phagocytosis signaling and cell migration (Takano et al., 2008), the malfunction of which can be a critical event in the development of malignant neoplasms. It is known that a high expression of FNBP1 is associated with highly invasive types of malignant neoplasms (particularly, breast, stomach, and bladder cancer) and correlates with a poor prognosis for patients (Wang et al., 2022). In this study, we investigated the mechanism of the formation of phagosomes with the involvement of Bcr and FNBP1 proteins. These data can reveal a potential role of Bcr-Abl and FNBP1 in phagocytosis and signaling of the cell and determine how a constitutive tyrosine activity of the oncoprotein contributes to the progression of CML.

MATERIALS AND METHODS

Cell culture. J774 cells were grown in the Dulbecco's Modified Eagle Medium (DMEM) (ThermoFisher Scientific, United States) with the addition of 10% fetal bovine serum (Sigma, United States), penicillin (50 units/mL), and streptomycin (100 μg/mL). The cell culture was maintained in an incubator at 37°C with 5% CO_2.

Cultivation conditions for *Saccharomyces cerevisiae*. *Saccharomyces cerevisiae* were cultivated in Dulbecco's Modified Eagle Medium (DMEM) (ThermoFisher Scientific, United States) with the addition of 10% fetal bovine serum (Sigma, United States) in a shaker incubator at 37°C for 1.5–2 h. The intensive shaking on a shaker incubator allowed to avoid the formation of yeast lumps. The *S. cerevisiae* cells were inactivated by incubation in a water bath at 65°C for 30 min and stained with propidium iodide.

Analysis of phagocytosis. Inactivated *S. cerevisiae* cells were added to J774 cells that reached 70–80% confluence at a macrophage/yeast ratio of 1 : 5. Phagocytosis was carried out for 1.5 h at 37°C in the presence of 5% CO_2. After this, J774 cells were thoroughly washed with PBS buffer and studied using immunofluorescence analysis.

Immunofluorescence analysis. J774 cells were fixed using 4% paraformaldehyde in PBS with 0.2% Triton X-100 for 20 min and blocked with 5% BSA in PBS buffer for 1 h. They were then incubated with primary antibodies to FBP17 (1 : 100, Santa Cruz Biotechnology, United States) and Bcr (1 : 200, Thermo Fisher Scientific, United States) for 1 h at a room temperature and with secondary antirabbit Alexa 647 (1 : 200 , ThermoFisher Scientific, United States), antimouse DyLight488 (1 : 200, ThermoFisher Scientific, United States) antibodies in the dark for 1 h at a room temperature. The cell nuclei were stained with DAPI for 2 min. To preserve the fluorescence, the preparation on the slides was polymerized using CitiFluor™ AF1, Mounting Medium (Science Services, Germany).

Confocal microscopy. Micropreparations were studied using a Leica SP8 scanning laser confocal microscope (Germany) using a 90° oil immersion objective with a numerical aperture of 1.3 in a sequential line scanning mode. A laser with a wavelength of 405 nm was used to excite DAPI, a laser with a wavelength of 488 nm was used to excite DyLight488, a laser with a wavelength of 532 nm was used to excite propidium iodide, and laser with a wavelength of 633 nm was used to excite Alexa647. The excitation and emission filters were installed in a Leica SP8 software in order to prevent cross excitation and spectral leakage.

Visualization and quantitative analysis of results. The images were processed using Fiji software. Gaussian blur with a radius of 1 pixel was applied to the images. After this operation, a deconvolution was performed in DeconvolutionLab 2 plugin using a Lucy–Richardson algorithm with a synthetic PSF on each channel. The number of deconvolution iterations was empirically selected to reach the best signal to noise ratio. The final montage of the images was performed in an EzFig plugin. Pearson correlation coefficient and Manders overlap coefficient were used for quantifying colocalization (Antonenko et al., 2020b), and the calculations were performed in a JACOP Fiji plugin.

Statistical processing of results. The diagrams were constructed using a ggplot library of R programming language in R. Studio integrated development medium. The results of the experiments are presented as arithmetic mean value with the standard error (±SE).

RESULTS AND DISCUSSION

In this work, using immunofluorescence analysis with subsequent confocal microscopy, it was demonstrated that FNBP1 is located within the absorption region of yeast cells during phagocytosis. The points of colocalization between BCR and FNBP1 were found in the phagosomes of J774 cells by overlaying two images (Fig. 1). We established that the Pearson correlation coefficient for colocalization between the BCR and FNBP1 proteins in J774 cells is 0.75 ± 0.05 ($n = 4$). The portion of BCR overlapping FNBP1 (Manders coefficient M1) is 0.70 ± 0.03 ($n = 4$), and the portion of FNBP1 overlapping BCR (Manders coefficient M2) is 0.63 ± 0.16 ($n = 4$), which indicates a high level of colocalization of BCR and FNBP1 proteins (Fig. 2).

Thus, based on the obtained experimental data, a new functional connection between Bcr protein and FNBP1 in macrophages was demonstrated, which allows to assert the effect of Bcr-Abl oncoprotein on FNBP1-mediated phagocytosis in chronic myelogenous leukemia cells. FNBP1 is a sensor protein of membrane tension and is able to change the level of

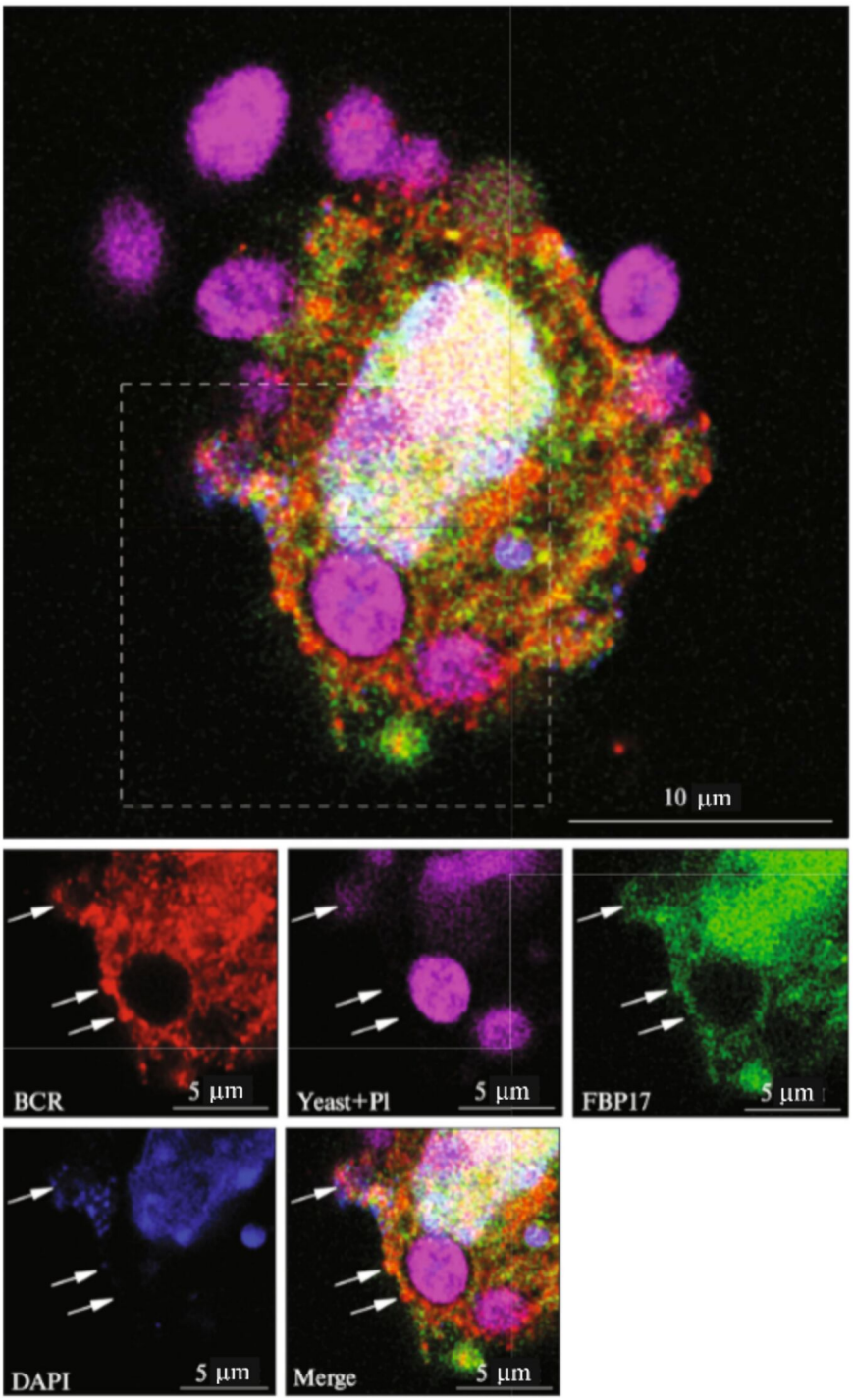

Fig. 1. Colocalization of BCR and FNBP1 proteins during phagocytosis in J774 cells. Immunofluorescence analysis using antibodies against BCR (red color) and FNBP1 (green color), overlapping of protein localization signals (yellow color). Yeast cells were stained with propidium iodide (purple color). DNA-binding fluorescent dye DAPI was used to visualize the nuclei (blue color).

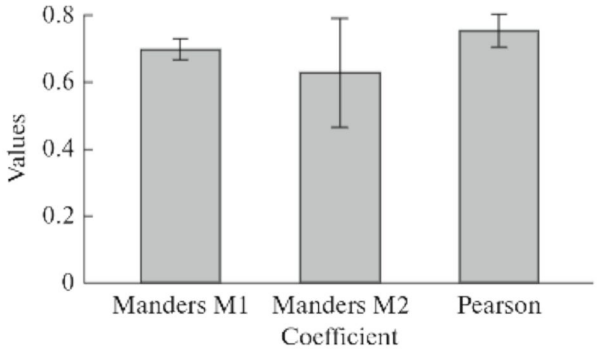

Fig. 2. Results of quantitative analysis of BCR and FNBP1 colocalization in J774 cells.

cell membrane tension and regulate its curvature (Yoon et al., 2021). FNBP1 in complex with CIP4 and TOCA-1 induces a rearrangement of the actin membrane-bound cytoskeleton, regulates receptor-mediated endocytosis, contributes to vesicle motility and membrane rupture (Kamioka et al., 2004; Suman et al., 2020). Through the activation of the N-WASP-WIP signaling pathway, the FNBP1 protein regulates the formation of podosomes and phagocytic cups required for macrophage migration. FNBP1-mediated membrane deformation with the involvement of dynamin-2 is an important condition for the formation of invadopodia (Wang et al., 2022). Phosphorylation, which can be an irreversible signal for the inhibition of its activity, is one of the key factors in the regulation of FNBP1. Thus, an increase in mechanical stress on the cell causes the FNBP1 protein phosphorylation by c-Abl kinase within the F-BAR domain, which, in turn, prevents FNBP1-dependent membrane bending and inhibits stress actin fibers (Echarri et al., 2019). In addition, Abl kinase is involved in actin rearrangement in the phagocytic cup by affecting the N-WASP protein with the involvement of other target proteins (Greuber and Pendergast, 2012). Taking into account FNBP1-dependent activation of N-WASP, it can be assumed that namely FNBP1 is one of such target proteins. The signaling pathway involving Abl kinase and FNBP1 underlies the coordinated functioning of the plasma membrane and cytoskeleton, which provides the cell stability and survival under stress conditions (Echarri et al., 2019). Therefore, uncontrolled phosphorylation of FNBP1 can have critical consequences for the development of malignant neoplasms and contribute to stress resistance and survival of cancer cells.

To date, knowledge about the role of FNBP1 in the development of malignant neoplasms is limited. A change in the level of FNBP1 expression is a typical feature of different types of cancer, particularly, breast, stomach, and bladder cancer (Yamamoto et al., 2011; Suman et al., 2020; Yoon et al., 2021). Molecular subtypes of breast cancer with a high level of FNBP1 expression are more aggressive and invasive and are characterized by a high level of malignancy, relapse, metastasis, and a poor prognosis for patients (Suman et al., 2018; Suman et al., 2020). FNBP1 regulates the formation of invadopodia, that is, protrusion of the plasma membrane rich in F-actin formed by invasive tumor cells that play a critical role in invasion with bladder cancer (Yamamoto et al., 2011). A high level of FNBP1 correlates with a poor survival of patients and is more common in diffuse histological type of stomach cancer, which is more prone to metastasis and is the worst prognostic factor (Yoon et al., 2021). A high level of FNBP1 expression is associated with deterioration in patients with glioma, squamous cell lung carcinoma, kidney cancer, and melanoma. Therefore, there is no doubt that FNBP1 can play a crucial role in the progression of some types of cancer (Wang et al., 2022). The localization of endogenous FNBP1 depends on the type of cells and forms of their existence, it can be found in different subcellular compartments, particularly, the plasma membrane, vesicles, and lysosomes (Yoon et al., 2021; Wang et al., 2022). In migrating cells, FNBP1 accumulates on short membrane invaginations at the leading edge during the membrane tension; after its decrease, they are randomly distributed throughout the cell (Tsujita et al., 2015). In the previous work, we detected the interaction between PH domain of the Bcr-Abl oncoprotein and FNBP1 in 293T cells (Gurianov et al., 2014).

A physiological role of the BCR protein is diverse and is determined by a large set of binding sites with other proteins, lipids, and its own enzymatic activity. Phagocytosis begins with the interaction of Fc receptors (FcR) located on the plasma membrane. In addition to FcR, complement receptors (CR) also trigger phagocytosis. Reorganization of the actin cytoskeleton is a necessary condition for the formation of a phagosome. This is promoted by Cdc 42, Rac, WASP, FNBI proteins, phospholipase C, etc. (Swanson and Hoppe, 2004). The resulting phagosome goes through a series of maturation events, acquiring the markers of early and late phagosome (Swanson and Hoppe, 2004). During phagocytosis, phosphatidylinositol-3-phosphate (PI(3)P) is generated, which is most abundant on early endosomes (phagosomes) and plays a crucial role in the recruitment of membrane effectors (Mayninger, 2012; Marat and Haucke, 2016). In the previous studies, we established that the PH domain of the Bcr interacts with a high affinity with phosphatidylinositols PI(3)P, PI(4)P, and PI(5) (Miroshnychenko et al., 2010). Due to this, its interaction with the phagosome membrane is assumed. Phagocytosis causes the cell protection from external pathogens by their destruction.

There are several ways to reach such effect. The production of reactive oxygen species (ROS) is one of the main ones. It sequentially includes the formation of a number of products, including superoxide radical

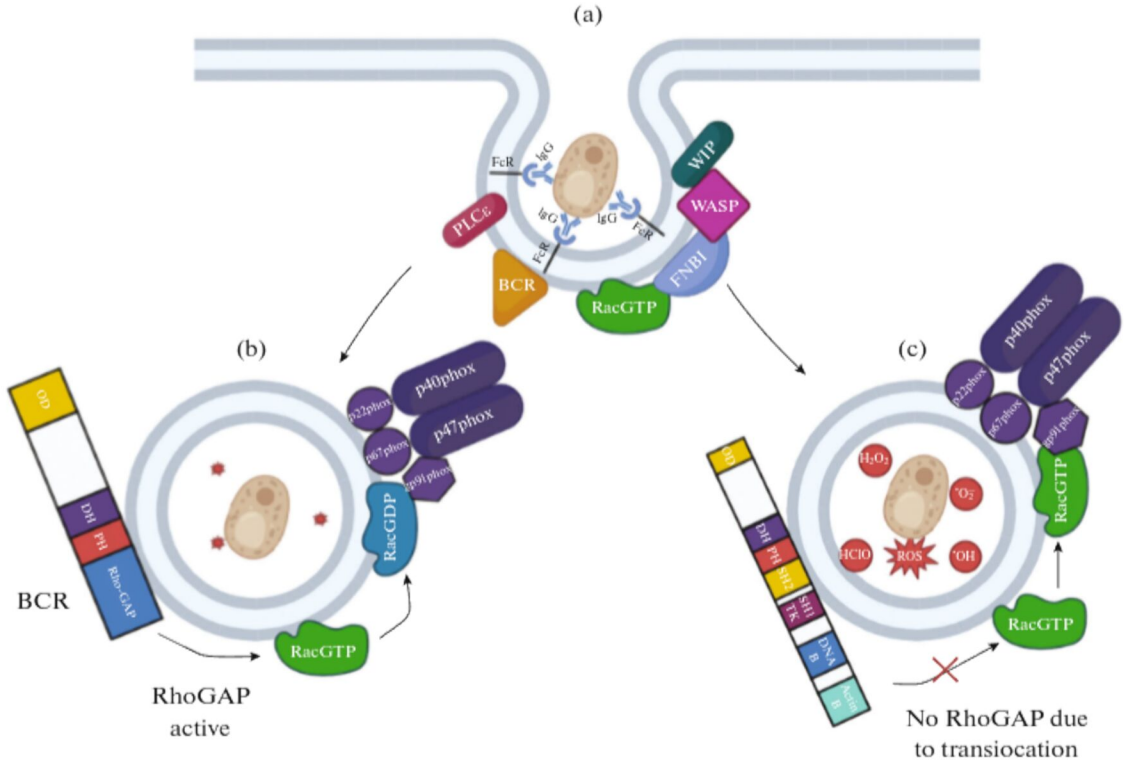

Fig. 3. Model of involvement of Bcr and FNBP1 in the formation of the phagosome and "oxidative burst." (a) Phagosome formation with the involvement of FNBP1; (b) the involvement of Bcr in the phagosome functioning, the presence of the GAP domain of the Bcr part negatively regulates Rac-GTPase, physiological level of reactive oxygen species; (c) the involvement of Bcr-Abl in the functioning of phagosomes, the absence of GAP domain of the Bcr part leads to uncontrolled Rac-GTPase activity (an increase in the level of reactive oxygen species).

(O^{2-}), hydrogen peroxide (H_2O_2), and hydroxyl radical (OH^-), and begins with the formation of a NADP oxidase complex. This complex consists of two membrane-bound subunits (gp91phox and p22phox (cytochrome b558)) and four cytoplasmic proteins (Rac, p40phox, p47phox, and p67phox) (Swanson and Hoppe, 2004; Utomo et al., 2006; Rodrigues et al., 2008). The well-coordinated work of the NADP-oxidase complex provides a decrease in pH inside the phagosome (as it occurs normally). A disruption of the regulation system (namely the activity of Rac GTPase) occurring, for example, in bcr-Null mutants leads to a so called "respiratory burst" (an excess in the production of reactive oxygen species) (Voncken et al., 1995).

The absence of a GAP domain (that is, a domain that reduces the activity of Rac GTPase in NADP oxidase complex) in the hybrid p210 Bcr-Abl protein leads to its constant activation (uncontrolled accumulation of ROS). This causes a further negative effect on the cell, contributing to the progression of the disease (acceleration) and the development of an acute phase (blast crisis) (Fig. 3).

Autophagy is one of the mechanisms for maintaining the homeostasis of malignant cells. BCR induces the expression of autophagy markers ATG3, LC3BII, and p62 at a protein level and ATG3 and GABARAPL2 at an RNA level in chronic myelogenous leukemia cells. BCR-mediated autophagy contributes to the survival of malignant cells, which negatively affects the therapy of chronic myelogenous leukemia (Smith et al., 2017; Smith et al., 2020). The mechanism of autophagosome formation is associated with the nucleation of actin, which is involved in different stages of autophagy, beginning from the formation of omegasomes and isolation membranes to the maturation of autophagosomes. The nucleation of actin has a formin-mediated nature. As one of the main nucleation factors, formin proteins control the formation of actin filaments in the temporal and spatial order, determining the diversity of actin structures and cellular processes, including autophagy (Coutts and La Thangue, 2016). Thus, a colocalization of the Bcr and FNBP1 proteins was confirmed and the subcellular localization of the Bcr/FNBP1 protein complex in the phagosomes of J774 cells was demonstrated. The results obtained demonstrated a new role for Bcr in FNBP1 phagocytosis of the cell and identify FNBP1 as one of the potential therapeutic targets in the treatment of chronic myelogenous leukemia. A model of

the effect of the Bcr-Abl oncoprotein on the formation of the excess of ROS in chronic myelogenous leukemia due to uncontrolled expression of phagosomal NADP oxidase is presented.

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COMPLIANCE WITH ETHICAL STANDARDS

The authors declare that they have no conflicts of interest. This article does not contain any studies involving human participants or animals as objects.

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