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Short Communication

Mechanotransduction and inflammation: An updated comprehensive representation

Vennila Suriyagandhi [a,1], Ying Ma [a,b,1], Veronica Paparozzi [a,1], Tiziana Guarnieri [a,c,1], Biagio Di Pietro [a], Giovanna Maria Dimitri [d], Paolo Tieri [a], Claudia Sala [e], Darong Lai [b], Christine Nardini [a,*]

[a] Consiglio Nazionale delle Ricerche, Istituto per le Applicazioni del Calcolo "Mauro Picone" (IAC), 00185 Roma, Italy
[b] Department of Computer Science and Engineering, Southeast University, 211189 Nanjing, PR China
[c] Department of Biological, Geological, and Environmental Sciences, Alma Mater Studiorum Università di Bologna, via Francesco Selmi 3, 40126 Bologna, Italy
[d] Department of Information Engineering and Mathematics, University of Siena, Italy
[e] Department of Medical and Surgical Sciences, Alma Mater Studiorum Università di Bologna, Bologna, Italy

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ABSTRACT

Mechanotransduction is the process that enables the conversion of mechanical cues into biochemical signaling. While all our cells are well known to be sensitive to such stimuli, the details of the systemic interaction between mechanical input and inflammation are not well integrated. Often, indeed, they are considered and studied in relatively compartmentalized areas, and we therefore argue here that to understand the relationship of mechanical stimuli with inflammation – with a high translational potential - it is crucial to offer and analyze a unified view of mechanotransduction. We therefore present here pathway representation, recollected with the standard systems biology markup language (SBML) and explored with network biology approaches, offering RAC1 as an exemplar and emerging molecule with potential for medical translation.

1. Introduction

Mechanotransduction is the event that consists of the conversion of mechanical into biochemical signal(s). Mechanotransduction is operated by a variety of cells and in a number of crucial events: from early embryonic development (epithelial mesenchymal transition, EMT type I[1]), to wound healing (EMT type II[2]) to the spread of metastases (EMT type III[3]) all all with a medically relevant counterpart in: experimental regenerative medicine;[4,5] dermatology for scarring and burning,[6] orthopedics for bone repair;[7] mechano-pharmacology;[8,9] and more rarely in a specific anti-inflammatory key.[10] Given this landscape, our ambition in this work is to trace the biological pathway that represents the transformation of mechanical cues into biochemical signals, with a specific focus on the intersection of this path with inflammation, i.e. the innate immune response, this being a less walked path, despite the fundamental role of inflammation in a variety of health-related conditions[11–13] and the potential for mechanical cues to modulate the immune response.[14,15]

Although numerous pieces of information are available in the literature, their integration is relatively limited.[16] This hampers the development of a systemic overview that is crucial to fully capture the potential and limitations of using mechanical stimuli to modulate inflammation, showing how some reactions, traditionally associated to mechanotransduction, produce in fact reactant traditionally associated to inflammatory pathways, thus blurring definitions and enhancing interoperability.

In fact, the identification of inflammatory markers as early actuators of mechanotransduction can offer insight into the potential of mechanical stimuli to directly impact on such markers and, similarly, the relation of anti-inflammatory targets with mechanotransduction can enable the design of mechanical therapies to strengthen the effects of pharmacological drugs.

One very effective frame to explore these interactions is the collection of information in a pathway, which exploits the network formalism. This allows to capture, rather than simplify, the complexity of a system, enabling the representation of multiple connections (edges of the

* Corresponding author.
E-mail address: christine.nardini@cnr.it (C. Nardini).
[1] These authors contributed equally to this work.

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network, biological reactions) among entities (nodes of the network, biological molecules).

This concept underpins the design of *in silico* pathways, enabling not only a faithful representation of the complexity of biological interactions, but also the exploitation of computational tools proper to the network theory (systems biology). This approach finally enables the identification of mathematically relevant nodes, whose biological importance has already been assessed.[17]

Therefore, building on our earlier work,[18] we have here curated a state-of-the-art representation of the pathway of mechanotransduction in relation to inflammation. This map is represented in a standardized format to ensure exportability, verifiability and expansion using the Systems Biology Markup Language (SBML[19]) and represents our main contribution: this carefully curated work offers, to the best of our knowledge -having screened the literature and popular and well curated repositories (Reactome,[20] Navicell,[21] KEGG,[22] Biomodels[23])-, the most complete, integrated and up-to-date collection of inflammatory pathways affected by mechanical cues. This is far from trivial, as it is known that in complex system some properties (named *emergent*) can be uncovered only when the system is studied in its entirety, rather than in simplified subsystems. In practice, this offers the possibility to identify molecules of potential medical interest that cannot be highlighted when exploring state-of-the-art inflammatory pathways representations (here, the innate immune response in Reactome).

As an exemplar result, in our analysis, RAC1, a non-preeminent target of anti-inflammatory therapies, emerges as an important molecule in the innate immune response, shall the system be subjected to mechanical forces, opening to further exploration of its therapeutic impact. This result is therefore a well-educated hypothesis on the opportunity for biomedical research to explore further the effectiveness of mechanical cues in modulating RAC1 activity, whose relevance in a number of diseases is well known.[24]

Our work also presents other types of analysis to offer a glimpse on the flexibility of use of such maps, including for instance indications and/or warnings on the differential functions that can be activated depending on the type of mechanical stimulus considered (*diffusion* analysis). This type of information can for example inform the testing and design of biomedical devices.

Overall, this mechanotransduction map represents a flexible resource to efficiently explore the translational potential of mechanical cues in medical applications. In the following, the terms network, pathway and map are used interchangeably.

Finally, it is worth mentioning that the careful process we followed to construct the map is based on manual curation, which implies lengthy preparation time. Given the state of advancement of AI, future work should consider large language models (LLM) as a potential means to accelerate such production. Certainly, such advances are conditioned by the training sets available, which are represented by manually curated results like the one presented in this work. In other words, therefore, future and faster advances are necessarily related to the ongoing production of carefully curated work.

2. Material and methods

2.1. Construction of the mechanotransduction SBML pathway

The *mechano core* map[18] has been updated with new entities from 12 recent (2015–2023) comprehensive review articles[6,14,15,25–33] and five research articles specifically related to the role of the aryl hydrocarbon receptor (AhR[34–38]), which, in addition to its recognized role as a sensor for endo- and xeno-biotics, has recently been recognized as having a role in the transduction of mechanical signals, particularly those associated with endothelial fluid shear stress and directional migration. Publications have been manually selected using the keywords “mechanotransduction”, “mechanical stimuli”, and “mechanical force”.

The map construction was done by manual curation translating natural language descriptions of molecules and reactions from the literature, into the standardized graphical representation of molecules (nodes) and reactions (edges) in the Systems Biology Graphical Notation (SBGN[39]) – i.e. the collection of biologically relevant biochemical entities (nucleic acids, simple chemicals, macromolecules, etc.) and reactions (production, inhibition, modulation, etc.), collectively called components, using CellDesigner.4.3,[40] which further operates the translation into SBML.

This representation is static, i.e. no kinetic parameters have been included in the representation, following Reactome,[20] Navicell[21] and KEGG[22] standard pathways representation. All components were updated with the standard MIRIAM (Minimal Information Requested in the Annotation of Models following-up on previously defined and accepted standards[41]) using the National Center for Biotechnology Information (NCBI[42]) gene IDs for genes and transcripts, Universal Protein Knowledgebase (UniProt[43]) ID for proteins and Chemical Entities of Biological Interest (ChEBI[44]) ID for small molecules, within the SBML *bqbiol:is* label. Entities with more than one ID were added to the *bqbiol:hasPart* element according to SBML rules.[45] Multiple proteins or genes with physical interaction are known as *complexes*, while multiple entities without physical interaction are known as *sets*. Sets are further divided in: *DefinedSet* (very general way of grouping molecules based on the fact that they share some common property, and often represent real complexes) and *CandidateSet* (way of grouping molecules when information is incomplete and one of several candidate physical entities is responsible for a particular task, indicating potential alternatives). This latter attribute were added to the *note*, to be fully compliant with Reactome.[20] Whenever literature was ambiguous a consensus discussion was held to identify the best representation/definition, and described in the *notes* to guarantee maximum traceability, transparency and reproducibility (see also Supplementary Materials for additional details).

When available, i.e. when sufficiently described, the specific nature of the stimulus has also been detailed, overall the map contains eight different stimuli including -beyond the generic (*inflammation*) and experimental inflammatory stimuli (lipopolysaccharide LPS *stress)- mechanical force*, *shear stress*, *stretch*, *stiffness*, *tension*, and *hydrostatic pressure*. Finally, the literature pertains to experiments conducted on multiple organisms. This information is stored in the CellDesigner *layer* attribute. Two versions of this map are available in the Supplementary Materials: MechanotransductionSBMLPathway_17.10.24 (pure SBML Level 2 Version 4) and MechanotransductionSBMLPathway_celldesigner_17.10.24 (CellDesigner file).

2.2. Construction of three mechano-inflammatory networks

The SBML format enables *systems biology* approaches to the study of mechanotransduction. In particular, pathways represented as complex networks can be manipulated (union, intersection to name a few). To perform these tasks we used Cytoscape[46] (Version: 3.10.1) with the cy3sbml app[47] to import the SBML file.

We first expanded the core mechanotrasduction network described above to include well known sub-pathways, i.e. we searched Reactome with the molecules identified in the explored literature for their corresponding (sub)pathway (P38, WNT, TGFB to name a few, see Table 1 for the full list). If a sub-pathway was present, it was attached to the core, via a union operation, given the recognized high quality of the Reactome project, to efficiently expand the neighborhood of our mechanotransduction map with existing and well assessed knowledge. We name this expanded network *Mechano-Union*.

We also defined a second network, by integrating the *Mechano-Union* to the Reactome Innate immune system (R-HSA-168249), this represents the expansion of the innate immune response to include also mechanical stimuli, in line with the idea of a *greater inflammatory pathway*[16] able to account for physical transduction. We name this network *Mechano-Innate*.

Finally, our third network was obtained by simply importing the Reactome *Innate immune system* pathway to use it as a baseline for comparison of network analyses (section 2.2). We name this network *Innate*.

Table 1
Subpathways of the Mechanotransduction pathway.

S.No	Reactome Pathway ID	Reactome Pathway Name
1	R-HSA-171007	p38MAPK events
2	R-HSA-195721	Signaling by WNT
3	R-HSA-983705	Calcineurin activates NFAT
4	R-HSA-2028269	Signaling by hippo
5	R-HSA-8878166	Transcriptional regulation by RUNX2
6	R-HSA-9006936	Signaling by TGFB family members
7	R-HSA-9013149	RAC1 GTPase cycle
8	R-HSA-5603029	IkBA variant leads to EDA-ID
9	R-HSA-75893	TNF signaling
10	R-HSA-1980143	Signaling by NOTCH1
11	R-HSA-1489509	DAG and IP3 signaling
12	R-HSA-166016	Toll like receptor 4 (TLR4) cascade
13	R-HSA-112409	RAF-independent MAPK13 activation
14	R-HSA-9818026	NFE2L2 regulating inflammation associated genes
15	R-HSA-8939211	ESR-mediated signaling
16	R-HSA-6783589	Interleukin-6 family signaling
17	R-HSA-194138	VEGFA-VEGFR2 pathway

All three Cytoscape networks are available as Supplementary material (MechanoUnion.cyjs used in Section Diffusion and MechanoInnate.cyjs, Innate.cyjs used in Section Topological Analysis), and a detailed example of construction is given in the Supplementary Material file.

2.3. Diffusion analysis

Network propagation or diffusion analysis was done using the *Diffusion* App of Cytoscape[46] and applied to the *Mechano-Union* map. Briefly, this analysis enables us to follow information fluxes (i.e. thermal energy accumulated on nodes) over time. In a translational perspective, this allows to explore how signals flow in the network, i.e. what are the final actuators of initial stimuli. For this reason, the analysis was run by setting an amount of energy solely on the node representing the stimulus of interest (one by one), and collecting the amount of energy that reached the nodes of the network at the end of the simulation, after heat had been transferred to the nodes encountered.[48] Results consist of a ranked list of the network nodes, with nodes having collected the highest amount of information/energy, ranking higher.

This type of output is well suited to perform an *enrichment analysis* which enables the identification of biological functions that are statistically significantly associated to the nodes that preserve energy: in other words, this allows the identification of the biological functions elicited by the stimulus.[49] This was done with R software version 4.0.4 and RStudio version 1.4.1106 by function *gsea*[49] in the Bioconductor Package *clusterProfiler*, and using the Hallmark[50] gene sets as functional references. Results' significance is corrected also by the number of tests (i.e. eight stimuli), to comply with the multiple hypothesis testing issue. Given that Hallmark gene sets and Reactome pathways do not use the same standard notation, we performed an automatic names conversion on all SBML pathways before importing them in Cytoscape.[46] Briefly, the MIRIAM identifier (see Section 1, Construction of the Mechanotransduction SBML Pathway) was converted with the biomaRt R package (version 2.46.3)[51] into the corresponding gene name. In particular we used the "hsapiens_gene_ensembl" reference, and within this set the "uniprot_gn_id", "entrezgene_id" and "external_gene_name", columns to extract the corresponding MIRIAM identifiers (Uniprot[43] and NCBI[42] for proteins, and for genes and transcripts, respectively) along with the name of the related gene.

This was applied automatically to simple molecules (i.e. not to sets) to 19 SBML files (the Mechano-Innate pathway, the 17 pathways in Table 1, and the Reactome Innate immune system (R-HSA-168249)).

2.4. Network topological analysis

Topological network analysis was run in Cytoscape[46] on the *Mechano-Innate* and the *Innate* networks, the rationale being to assess what differences emerge, shall we consider "classical" immune response (*Innate* network) or also the mechanotransduction phenomenon (*Mechano-Innate* network) as an activator of immunity.

Preprocessing involved the removal, given their ubiquity, of the small molecules which include: H_2O, ATP, ADP, GTP, GDP, H^+, Na^+ and Ca^{2+}, as their high connectivity biases the topological analysis, ranking them excessively high in topological network analyses. Further the corresponding cytoscape.JSON files were exported and the topological analysis was run with Python 3.8 and the *NetworkX*[52] package to create directed graphs, a manipulation necessary to convert the JSON files that have species' nodes connected to reaction nodes, into a network where species are represented in nodes and reactions in edges. This was achieved as follows: species nodes with identical names (i.e. phosphorylated and non-phosphorylated version of the same molecules as well as, genes, transcripts and protein of the same molecule, to avoid their over-representation in topological terms) were merged and new edges between species nodes connected via the same reaction node were created, to preserve the biological pathway's structure. Finally, on these structures, topological analysis was applied to compute four *centrality* measures: *closeness* indicate how close a node is to all other nodes; *betweenness* indicates the highest number of shortest paths (number of edges connecting two nodes); *degree* indicates the number of connected nodes and *eigenvalue* centrality gives a measure of the connections to nodes that have high connections.

Finally, we compared, for the molecules shared between the two networks, the centrality measures. We retained the nodes whose differences were the highest (across all four measures, as a proxy for robustness), since they represent molecules whose impact on immunity changes most, shall we consider mechanical stimuli as relevant in triggering an immune response. Therefore, this analysis lets emerge the molecules whose centrality changes most when considering mechanotransduction as an integral part of innate immunity, thus identifying molecules whose relevance might be overlooked as inflammatory targets, while they may become relevant when the system is perturbed by mechanical stimuli.

3. Results and discussion

3.1. Mechanotransduction map

The SBML file is available in the Biomodels[23] repository, with all future extensions and updates being there available, with ID MODEL2406110001 (https://www.ebi.ac.uk/biomodels/MODEL2406110001).

3.2. Diffusion analysis

The diffusion analysis allows us to gain insight into the steady state (i.e. late) effect of a network perturbation, in our case the different types of mechanical stimuli. In particular, a given amount of energy (heat) is let to flow over time (simulation steps) across the network. According to the specific wiring of the network a reduced amount of the original energy (consumption) is being transported towards connected nodes, while avoiding nodes that are not reached before the exhaustion of this energy.

Results come in the form of a list of all network molecules and their accompanying heat (Supplementary Material, Table S1 Diffusion). This type of information is appropriate for an enrichment analysis, and in particular, *hot* molecules represent high ranking genes (or associated proteins) that can be processed by gene set enrichment analysis[49] (see Methods) to identify which functions are majorly (and possibly differentially) affected by the stimuli. Fig. 1 shows the results of the enrichment analysis (See also Table S2 Supplementary Material), indicating that in general all stimuli are statistically significantly enriched for inflammatory (p.e. TNFA signaling via NFKB, TGF beta signaling, IL6 JAK STAT3 signaling, IL2 STAT5 signaling etc.) and proliferative (WNT BETA catenin signaling, Epithelial Mesenchymal Transition, G2M Checkpoint etc.) functions, explicitly listed in the rows of the dot plot in Fig. 1. These

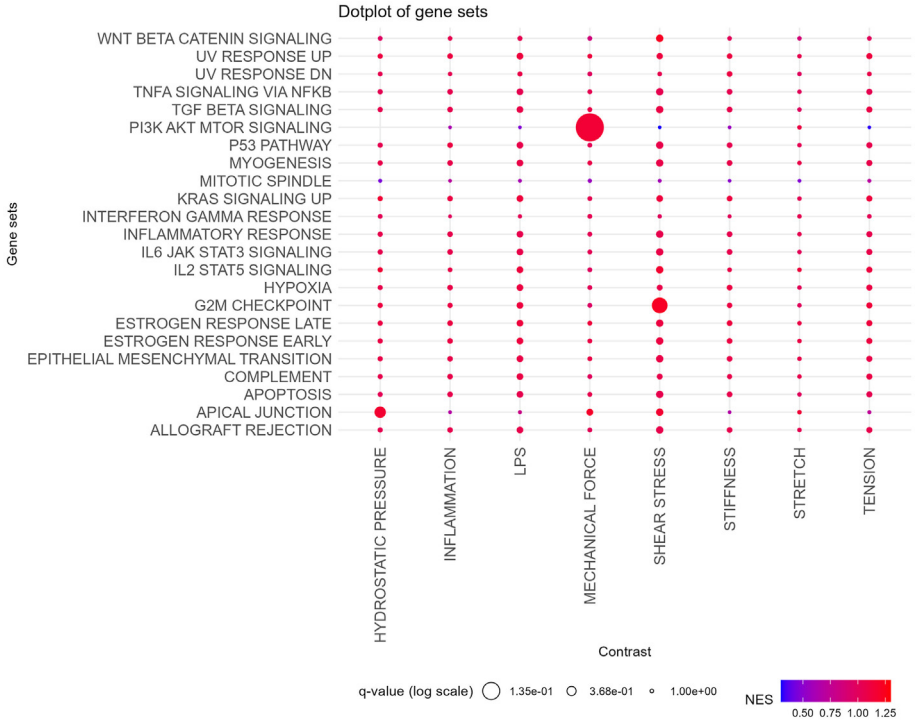

Fig. 1. Enrichment analysis (by GSEA) of the network genes ranked by heat, upon diffusion analysis. The functions on the vertical axis correspond to enriched Hallmark functions, while the horizontal axis reports the elicited stimulus. The size of the dots is inversely proportional to the statistical significance of the enrichment.

Table 2
Immuno-mechano complexes.

Node Complex Name	Group
2x DDX58 ligand:2x DDX58:2xATP [cytosol]	**Pathogens**
Activated TAK complexes [cytosol]	
STING:TBK1:IRF3 [cytoplasmic vesicle membrane]	
TAK1 complex [cytosol]	
UBE2N:UBE2V1 [cytosol]	
WRC:IRSp53/58:RAC1:GTP:PIP3 [plasma membrane]	
CHUK:p-S177,S181-IKBKB:IKBKG [cytosol]	
Clustered IgG-Ag:p-FCGRs [plasma membrane]	
Clustered IgG-Ag:p-FCGRs:p-6Y-SYK [plasma membrane]	
dsDNA:ZBP1:pS-172-TBK1 [cytosol]	
IKBKG:p-S176,S180-CHUK:p-S177,S181-IKBKB [cytosol]	
Mother filament:branching complex:daughter filament [cytosol]	
NLRP4:DTX4:dsDNA:ZBP1:pS-172-TBK1 [cytosol]	
NLRP4:DTX4:STING:p-S172-TBK1:IRF3 [cytoplasmic vesicle membrane]	
p-S,2T-IRAK4:oligo-MyD88:TIRAP:activated TLR receptor [plasma membrane]	
DAGs [plasma membrane]	**Lipids**
PI(3,4,5)P3 [plasma membrane]	
PI(4,5)P2 [plasma membrane]	
PPi [cytosol]	
DAP12 Receptors:p-DAP12:p-6Y-SYK [plasma membrane]	**DAP12**
p-5Y-LAT:GRB2:SOS1:GADS:p-Y113,Y128,Y145-SLP-76:PLCG:VAV:BTK:PIP3 [plasma membrane]	
p-5Y-LAT:p-SHC1:GRB2:SOS1:GADS:p-Y113,Y128,Y145-SLP-76:PLCG [plasma membrane]	
NFKB1(1-433), NFKB2(1-454):RELA [cytosol]	**NFKB**
NFKB1:MAP3K8:TNIP2 [cytosol]	
p-S32,36-IkB-alpha:NF-kB complex [cytosol]	
Active NIK:p-S176,180-IKKA dimer [cytosol]	
Clustered p:LYN:p-FCERI:IgE:allergen:p-6Y-SYK [plasma membrane]	**FCERI**
p-4S,T404-IRF3,p-S477,S479-IRF7 [cytosol]	
Allergen:p-LYN:p-FCERI:IgE aggregate [plasma membrane]	
p-5Y-LAT:p-SHC1:GRB2:SOS1:GADS:p-Y113,Y128,Y145-SLP-76:PLCG1:VAV [plasma membrane]	
K63polyUb [cytosol]	**Innate immune**
Activated TLR4:TRIF:K63polyUb-TRAF3:K63polyUb-TANK:p-TBK1/p-IKBKE [endosome membrane]	
CALM1:4xCa2+ [cytosol]	**CALM1**
RAC1:GDP [plasma membrane]	**RAC1**

functions are broadly in line with the wound healing process (or EMT type II[53]) which proceeds across an early and transient inflammatory phase and evolves towards regeneration (requiring proliferation) and further remodeling.

It is nevertheless interesting to observe that, beyond these common functions, some specific patterns can be observed. Not surprisingly, *inflammation* and *LPS*, at this granularity of modeling, indicate a relatively uniform activation of all the functions identified. Conversely, *mechanical force*, which represents the indistinct mechanical stimulus that was modeled in our previous work[18] shows a visible enrichment on the tumor associated *mTOR pathway*,[54] this is in line with the literature that was adopted for that reconstruction, which turned out to have a particular emphasis on EMT type III. This bias was among the motivations to update our network with the current work.

Finally, regarding the specific types of mechanical forces included in our model, we can observe few peculiar patterns. The first is concerned with *hydrostatic pressure* which elicits more specifically *apical junctions* (formation), a results that, if experimentally validated, could expand the information reported from the original literature.[38] The second regards *shear stress*, where the activity concerned with the *GM2 checkpoint* appears to be the most enriched. Interestingly we can also observe that mechanical *stretch* appears to elicit the same overall functions but with lower significance, suggesting, in this sense, a milder efficacy of this type of stimulus.

3.3. Topological analysis

Topological analysis allows the identification of important nodes, where importance is defined based on the ability of such nodes to connect the network. The most assessed metrics to compute this importance include the *degree*, *betweenness,* and *stress centrality* and the *eigenvalue*. In our analysis we computed all statistics to obtain a list of molecules whose importance is dramatically different when computing it in the Innate only or in the Mechano-Innate. We here discuss the role of these molecules and do so after selecting the more robust, i.e. the molecules that change their importance across all four measures (full list and metrics in Table S3, Supplementary Material).

The full list of these thirty-four nodes (named *immuno-mechano complexes*) is available in Table S4 of the Supplementary Material, where we also list their description as retrieved from Reactome by manual curation, and further grouped in six main areas of activity, in Table 2. The first group pertains directly (and generically) to the response to pathogens. The second has to do with membrane lipids, this is not surprising, as it is well known that mechanical transduction consists of the activation of receptors by physical stress of the membrane and/or the extracellular matrix. Similarly we observe that the third group has to do with well-known key molecules including Nuclear Factor kappa-light-chain-enhancer of activated B cells NF-κB,[55] *Transmembrane Immune Signaling Adaptor (TYROBP)* known as DAP12[56] and interferons (IFNα, IFNβ). Finally, we highlight RAC1 and CALM1, two specific molecules, whose biological role is known to be crucial in the regulation of ion signaling. While CALM1 mechano-mediated effects are less explored and so is its role as drug target,[57] RAC1 (with RhoA) is a well-known key player in mechanotransduction.[58,59] Its relevance in inflammation is also known, and the modulation of RAC1 in numerous diseases from allergies[60] to cancer[61] is recognized.

From a topological standpoint, the relevance of these molecules appears to be coherently increased across all measures of centrality (in the plasma membrane and in the cytosol, respectively, see Supplementary Material Table S3). This indicates that these molecules, when considering the effect of a mechanical stimulus on the inflammatory state of the system, have the potential to connect to other molecules (eigenvalue, closeness and degree) with an efficiency (betweenness), that is higher than what has been recognized so far, when inflammation was reduced to its more classical innate immune response definition.

What we offer with our investigation is therefore the recommendation to explore the potential of constraining RAC1 (and CALM1) activity with mechanical stimuli, as this and similar approaches (see for instance the modulation of Ca^{2+} ion channels by magnetic stimuli[62]), can efficiently complement pharmacological research and drug design.

CRediT authorship contribution statement

Vennila Suriyagandhi: Writing – original draft, Data curation. **Ying Ma:** Writing – original draft, Formal analysis. **Veronica Paparozzi:** Writing – original draft, Formal analysis. **Tiziana Guarnieri:** Writing – original draft, Formal analysis. **Biagio Di Pietro:** Visualization, Formal analysis. **Giovanna Maria Dimitri:** Formal analysis. **Paolo Tieri:** Formal analysis. **Claudia Sala:** Formal analysis. **Darong Lai:** Methodology. **Christine Nardini:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Formal analysis, Conceptualization.

Ethical approval

This study does not contain any studies with human or animal subjects performed by any of the authors.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mbm.2024.100112.

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