Wound Healing from Bench to Bedside: A PPPM Bridge Between Physical Therapies and Chronic Inflammation

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Abbreviations

ACR	American College of Rheumatology
AP	Acupuncture
CIA	Collagen induced arthritis
DAS	Disease activity score
EMT	Epithelial-mesenchymal transition
ERAS	Early recovery after surgery
EULAR	European Alliance of Associations for Rheumatology
GI	Gut Intestinal
GIP	Greater inflammatory pathway
HAQ	Health assessment questionnaire
LLLT	Low level laser therapy
MTX	Methotrexate
NCD	Non-communicable diseases
PBMC	Peripheral blood mononuclear cells
PBMT	PhotoBioModulation therapy
PPPM	Predictive, preventive, personalized medicine
RA	Rheumatoid arthritis
RF	Rheumatoid factor
SGD	Sustainable development goal
UN	United Nations
VNS	Vagal nerve stimulation
WH	Wound healing

1 Introduction

1.1 Inflammation

Inflammation is known to correlate with the majority of maladies we are not yet able to cure, with particular emphasis on non-communicable diseases (NCDs), responsible, worldwide, for 44 million deaths per year [1], and in Europe for 80% of expenses associated with disease [2]. The societal impact of this silent pandemic is so vast that the United Nations (UN) have recognized it as one of the 17 major obstacles to our sustainable development, and have proposed the Sustainable Development Goal (SGD) 3 to be specifically concerned in target 4 with NCDs and mental health (SGD3.4: "By 2030, reduce by one third premature mortality from non-communicable diseases through prevention and treatment and promote mental health and well-being").

In the past 10–15 years, numerous discoveries have contributed to enlighten our understanding of inflammation, including the activity of the autonomous nervous system in the control of inflammation, namely the *inflammatory reflex* [3–5], the role of the gut intestinal (GI) [6, 7] and oral [8] microbiomes. PPPMs approaches have promoted the relevance of assessing chronic inflammation and wound healing gone awry [9], two accompanying phenomena to the development of NCDs, with a long prodromic phase where subclinical inflammation plays a silent yet fundamental role [10].

It descends from these considerations that a better understanding and, importantly, a better control of inflammation must consider as many factors impinging on inflammation as possible. Our theoretical pioneering effort in this direction presents the *Greater inflammatory pathway (GIP)* [11] as the *summa* of such influences, and updates the definition of the pathway(s) whose alterations should be studied to control inflammation, including namely: the autonomous nervous system, the host–microbiome interface, and wound healing. In this frame and further [12], we have already observed that, while the recent attention on the GI microbiota and the inflammatory reflex have promoted experimental therapies ranging from *fecal transplant* [13] to vagal nerve stimulation (VNS) in bioelectronic medicine [14], respectively, therapeutic *physical stimuli (*i.e.*, exploiting electric, optic, magnetic or mechanic stimuli*), which directly elicit WH, remain among the most neglected research areas.

Wound Healing (WH)-also known as epithelial-mesenchymal transition (EMT) type 2- progresses from a transient inflammatory phase, through regeneration to remodeling [15]. Its known paracrine effects are also accompanied by long distance consequences, as shown by our original work [16] and few others [17, 18], but poorly, if at all, translated into medical practice.

1.2 Recollecting a Compartmentalized and Scattered Knowledge Related to Physical Stimuli on Inflammation and Wound Healing

Indeed, research on the effects of physical stimuli on inflammation is very uneven, depending mostly on the nature of the stimulus. In fact, ample disparities exist in terms of quality and quantity of the basic biological knowledge available.

Recognizing and recollecting this scattered scientific background is the first necessary step to promote additional access to anti-inflammatory therapies, and complete the *bench* step.

1.2.1 Mechanical Stimuli

Mechanical stimuli (such as, but not limited to, vibrational therapy [17], manual acupuncture [16], massage [19, 20]) are well known to elicit all stages of WH, indeed, "injuries" are mostly thought of as mechanic. Mechanosensing and mechanotransduction are the cellular phenomena at the basis of this effect, and all cell types are known to present both these features. There exists extensive knowledge on their temporal and biochemical functional activation, including the complex transcriptional and phenotypic changes supported at the cellular level [21–23], recapitulating the inflammatory, remodeling and regenerative phases of WH. Generally, however, despite good to excellent biological knowledge of EMT type2, mechanical stimuli quantification for WH therapeutic elicitation remains empirical and translation has not proceeded to the clinics, despite relevant potential application in oncology [24] and results in muscle regeneration [25] for instance, and with the exception of the exploitation of the events occurring in the regeneration and remodeling phases (regenerative medicine), but very seldom in relation to the inflammatory phase, despite few exceptions [16–18].

1.2.2 Electric Stimuli

Electric stimuli have also received ample attention, owing to different theories that imply the usage of electricity to restore a variety of physiological features. The sensitivity to electricity of neural cells is likely the best assessed, from L. Galvani [26] onwards. Recently, as briefly introduced above, this knowledge has been expanded with a novel understanding of the effects of electrical stimulations during inflammatory episodes i.e. by *bioelectronic medicine*, where the *inflammatory reflex* [3, 5] has recently been uncovered and describes the negative feedback loop that is activated by the autonomous nervous system (ANS) in case of acute [27] and chronic [28] inflammation to control cytokines production and dampen inflammation. Electricity is also important in a different context, relevant to our purposes, as it is known to interfere with superficial wound healing. This is based on the "skin battery" concept [29–31], i.e., the difference of potential that exists in healthy and integer skin, and that is disrupted in case of physical injuries, braking the skin barrier and hence compromising the organized electrical charges that exist inside, differentially from outside, this barrier. In this case, appropriate electrostimulation (i.e., direct and of the magnitude of the skin battery) is experimentally proven to restore physiological conditions, and is known to be accompanied by improved WH (skin regeneration and remodeling), with explicit usage in dermatology and orthopedics. At the cellular level electrosensing and electrotransduction are embodied by lipid rafts [32], whose mobility within the cells' surface polarizes the membrane, deforming it with consequences that are likely to mimic mechanotransduction ones.

1.2.3 Optical Stimuli

Optosensitivity and optotransduction at the molecular and cellular level, originally emerged, similarly to electrostimulation, in a specialized context, i.e., associated to the photoreceptor cells of the retina. Nevertheless, the actuator proteins, *optins*, have also been found in fibroblasts and keratinocytes, leading the way to the exploitation of optical stimuli on the largest of our organs: skin (dermal photoreception) [33, 34]. **P**hoto**b**io**m**odulation (PBMT) is the corresponding **t**herapeutic approach, i.e., the effect of optical signals at the organ(ism) level, generally offered as low-level laser therapy (LLLT). Despite abundant work on the application of such stimuli [35, 36], there exists very limited available literature on the explicit anti-inflammatory outcome of LLLT, reported as secondary effects (i.e., secondary to the light transduction) in the form of small molecules flux changes that do overlap exactly the non-transcriptional phase of mechanostranduction [37] (but not made explicit nor recognized as such), and as tertiary effects in terms of remodeling and regeneration. Very recently the relation between the *aryl hydrocarbon receptor* and optical stimuli has been uncovered, hopefully opening to a deeper and broader understanding of the connection with inflammation [38]. Laser applications are better known for their applications in surgery, with the majority of other types of application left to unstandardized approaches, mostly in the realm of complementary alternative medicine. Overall, at all scale levels (molecules, cells, tissues, organism) rigorous effects of optical stimuli are poorly represented.

1.2.4 Magnetic Stimuli

Magnetic stimuli are by far the most neglected in biomedicine. The usage of magnetic fields in relation to biology is in fact more commonly focused on the growth of organic crystals, using high levels of energy. Robustness of the available information is weakened by the variability of the magnetic field parameters adopted. Recent detailed work refers to mechanomagnetic [39] effects, directly indicating that the cascade of events following this type of stimulation replicates WH, other less recent results clarify the effect of static magnetic field, highly cell-dependent [40], overlooking mechanical aspects and their effects on channels, membrane, as well as Ca^{2+} fluxes change, overlapping, although generally unrecognized, with the progression of WH.

All the above information is the result of the careful collection from a large variety of publications in different research areas that remain strongly compartmentalized and rarely speak to each other (from engineering to physics to biology and biomedicine). In addition to this "horizontal" compartmentalization (related mostly to the different nature of the stimulus) there exists also a striking "vertical" compartmentalization, i.e., there is limited to no connection among the findings at the cellular level and their impact on higher scale complexes like tissues, organs and finally the human body. This vertical compartmentalization holds independently of the biological background: therapeutic dose is fully empirical based solely on the *do not harm* principle and, importantly, only rarely the medical rationale builds on the biological work, despite a large variety of attempts to exploit -in a mostly unstructured manner- physical stimuli.

2 Working Hypothesis

To move beyond this fragmentation, we hypothesize that WH can be the target phenomenon and function able to recollect under one common and complex concept the effects of therapeutic physical stimulations. In particular, knowing that WH is a highly conserved function elicited by physical stimuli and that under physiological conditions the early inflammatory phase has a transient nature, we hypothesize that purposedly eliciting this inflammatory phase by controlled physical stimuli may first elicit and then force the extinction of inflammation, not only in physiologic but also in inflamed contexts. To test our hypothesis we chose rheumatoid arthritis (RA) a model NCD whose impact on health and societal expenditure is recognized as dramatic [41]. The international organisms promoting guidelines for the control of RA (American College of Rheumatology, ACR, and the European Alliance of Associations for Rheumatology, EULAR), recommend to maximally anticipate the diagnosis of the disease [42, 43], in line with the paradigm of predictive, preventive, and personalized medicine (PPPM) [44] that promotes the identification and treatment of *ALL* inflammatory symptoms as early as possible, to minimize the devastating progression of NCDs. Moreover, International recommendations envision the use of classic and biologic disease modifying anti-rheumatic drugs (*c*- and *b*DMARD, respectively) until clinical remission (i.e., stabilization of the symptoms) with the possibility of subsequent DMARDs tapering and discontinuation [43].

3 Methods

We tested this hypothesis in a multiscale context, with animal model studies [16, 45] and a human pilot clinical trial [46] (NCT01619176, https://clinicaltrials.gov/ct2/show/NCT01619176) with the aim to assess the extent of our results' translatability.

3.1 Animal Studies

Collagen induced arthritis (CIA) [47] is a known model of RA induced in animals, recapitulating the majority of immunological and phenotypic alterations of RA. Our two studies, on Wistar rats, include control and active arms, where methotrexate (MTX), the gold standard DMARD therapy, is adopted, and mechanical stimulation [48] is performed by insertion and rotation of thin needles (acupuncture -AP) alone or in combination with MTX (MTX + AP). Phenotypic assessment of the disease was done with standard approaches (paws thickness by qualitative visual scale and quantitative with a gauge). Multiple samples from different tissues (blood peripheral blood mononuclear cells -PBMCs-, stool, subcutaneous tissue and rheumatoid arthritis fibroblast like cells -RAFLs-) and at various time points (before, at 1 h, 14 days and 32 days from the beginning of the therapy) were collected and

processed with omics (miRNA, mRNA for blood and subcutaneous tissue sample, 16S-rRNA-seq for GI microbiota analysis), with all details, including therapeutic release and raw data availability, being reported in [16, 45] and summarized to explore translatability in Fig. 1.

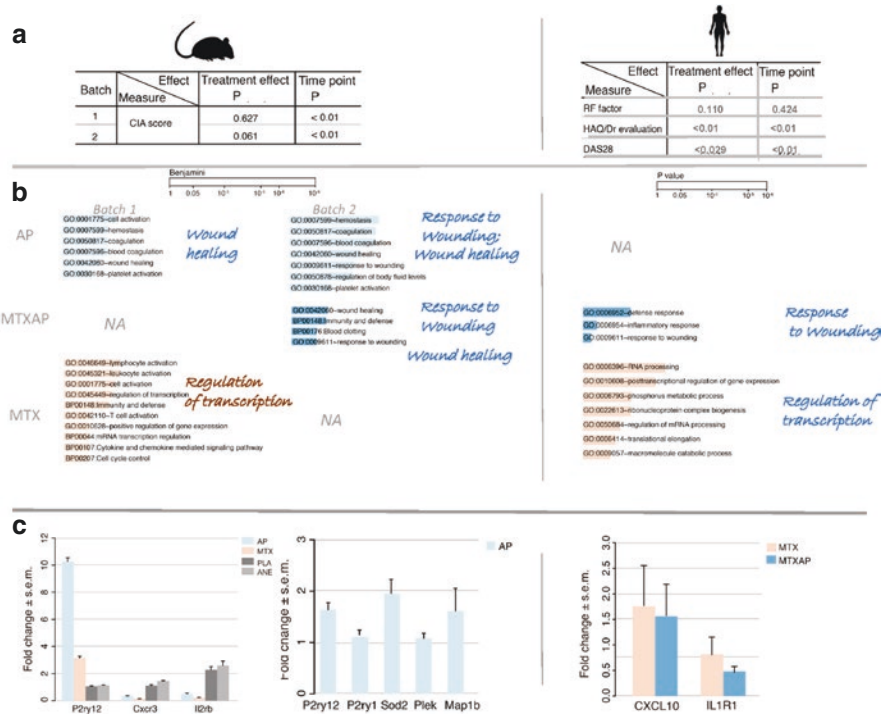

Fig. 1 Translational results, continuum between animal models (rats) and humans. Analyses were run using R version 3.6.2 or later. Panel **a**: Statistical analysis of clinical standard data, *P* indicates *p*-values based on the F-distribution. Panel **b**: blood functional results (Gene Ontology Enrichment) across batches and species including animal studies (batch1 and batch2) and the pilot human clinical trial ID: NCT01619176A, https://clinicaltrials.gov/ct2/show/NCT01619176. Blue and red bars across enriched functions indicate the associated (corrected) *p*-values for up- and down-regulated expression, respectively. Summary enriched functions are reported for enhanced clarity (handwritten style). All animal results were published in [16, 45]. Human data were aggregated to compensate for the small samples size. Namely: 18 blood samples from 9 RA patients in total, 8 before any therapy (RA), 2 AP after 2 week (AP), 5 AP + MTX after 3 months (MTXAP), 3 MTX (MTX) after 3 months. NA stands for "not available," i.e., this branch of the study was not performed. Panel C: Independent qRT-PCR analysis s.e.m. = standard error of mean. The genes studied were: Purinergic Receptor P2Y12 (P2ry12), C-X-C Motif Chemokine Receptor 3 (Cxcr3) and Interleukin 2 Receptor Subunit Beta (Il2rb) for batch 1; P2ry12, Purinergic Receptor P2Y1 (P2ry1), Superoxide Dismutase 2 (Sod2), Plekstrin (Pleck) and Microtubule Associated Protein 1B (Map1b) for batch 2; C-X-C Motif Chemokine Ligand 10 (CXCL10) and Interleukin 1 Receptor Type 1 (IL1R1) for the huma pilot trial. Rat and human icons by Freepik from www.flaticon.com

3.2 Pilot Clinical Trial

We designed a pilot study, approved by the ethical committee of Shanghai GuangHua Hospital, designed as a non-inferiority trial where 10 RA patients were enrolled, balanced by age, uniformly treated with leflunomide and non-steroidal anti-inflammatory drug and randomly assigned to MTX or AP only for the first 2 weeks and to a combination of the two (MTX-AP) or continuation of MTX alone, for 3 months in total. Details on both therapy dose and stimulation points can be found on clinicaltrials.gov, ID: NCT01619176, https://clinicaltrials.gov/ct2/show/NCT01619176. Clinical parameters for enrollment and monitoring were collected according to the American College of Rheumatology (ACR) guidelines and include Rheumatoid Factor (RF), patients and clinicians Health Assessment Questionnaire (HAQ) and DAS28 scores. Statistical phenotypic data analysis for ACR recommended parameters [49] (RF, HAQ and DAS28) was done modeling the parameters as functions of treatment and time (beginning of therapy, 3 weeks, 3 months), with fitted generalized linear models and analyzed by ANOVA (RF, DAS28) and MANOVA (HAQ). Omics were collected for assessment of the systemic effects of the therapy via blood samples (peripheral blood mononuclear cells, PBMC) processed by transcriptomics. PBMCs were analyzed via Affymetrix U133 plus 2.0 array (Gene Expression Omnibus repository, *ID* GSE59526, https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE59526) with the following specifics: expression intensities and calls detection filtered for the removal of probes with less than 10% of all samples, log-2 transformed and selected as differential (end of therapy samples versus all before therapy samples) with *limma* [50] for p-value <0.05 and fold-change >1.8. Further candidates for which 30% of expression intensity across all samples was absent for detection call were also removed. Functional enrichment analysis was run with DAVID functional cluster analysis [51].

For all organisms' studies, validation with an independent technology was run by qRT-PCR (Fig. 1c).

4 Results

The continuum of phenotypic and molecular data analysis results are shown in Fig. 1, where side-by-side comparison of PBMC transcriptomics highlights the translatability of the findings and the crucial involvement of WH as statistically significantly enriched function across the two organisms and the three studies, when comparing the role of the mechanical stimulation on (model) arthritis.

In particular, with respect to the human data, the phenotypic statistical analysis returned significant treatment and timepoint effects for DAS28 and qualitative results (HAQ pooled with clinicians' evaluation) – (values for MTX lower than for MTX-AP). Despite RF factor reducing over time and values for MTX being higher than for MTX-AP, due to a lack of power (missing data at multiple timepoints), the RF analyses did not return significant results (Fig. 1a). Phenotypic results are backed by the search for molecular surrogates via PBMC differential and functional

analyses (Fig. 1b). The only enriched cluster (enrichment score > 1) is shown for human MTXAP2RA (MTX + AP versus baseline) comparison and all top terms (GO hierarchy) from the MTX2RA (MTX versus baseline) seven enriched clusters are shown. A similar analysis was run on animal models with detailed adaptation of the protocol and analysis reported in [16, 45]. This highlights overall the relevance of wound healing as the distinctive function elicited in the presence of the mechanical stimulation (AP), alone or in conjunction with the gold standard treatment.

5 Conclusion and Recommendations

We present, for the first time, two fundamental steps in the advancement of our knowledge on the therapeutic potential of physical stimuli. First, the introductory overview and revisitation on the shared biological functions activated by physical stimuli, independently of their nature, in an anti-inflammatory context, is to the best of our knowledge a première in this direction. Second, the continuum of systemic (PBMC) molecular effects descending from a therapeutic mechanical stimulus in a chronic inflammatory context represented by (model) arthritis, shows how this function is conserved.

The first step serves the second not only in the progression from bench (basic science) to bed (animal/clinical studies), but also from a theoretical perspective given the fact that all stimuli appear to proceed by the activation of mechanotransduction typical markers (see above, under Sect. 1.2): in this sense the loss of generality in our experiments using mechanical stimuli (i.e., manual AP) could be minimal, considering also that RA is a model NCD.

Globally, our results show that the proposed therapy progresses (also) via the elicitation of the function of *wound healing*, a transversal phenomenon, crucially impacting on the control of inflammation as we recently discussed within the transversal basic science frame of the Greater Inflammatory Pathway [52]. Such findings are relevant in the context of the ERAS ecosystem, whose evidence-based guidelines/protocols (see https://erassociety.org) are crucial for PPPM, and with particular emphasis on generally neglected clinical matters like prehabilitation, pain chronification prediction, mitochondrial health and suboptimal health, to name the major.

6 Expected PPPM Impacts

Our results, although plagued in the human study by the small sample size, represent nevertheless a fundamental starting point to explore the rationale (fundamental biology, *bench*), reproducibility (clinics, *bed*), and reimboursability (health policy, PPPM) of physical therapies. This tangible expression of the anti-inflammatory potential of the elicitation of wound healing can offer a biomedical rationale to exploit a variety of physical therapies, rapidly expanding the arsenal of approaches available to control overt and pre-clinical chronic inflammation, at the base of all

NCDs [9]. This is in line with the aforementioned ERAS initiative, which aims at promoting evidence-based best-practices for effective personalized approaches. As a consequence, conclusions for experts including all stakeholders in the rich PPPM ecosystem include **two major recommendations:**

The first is to take maximum advantage of existing basic biological (molecular and cellular) knowledge when it comes to physical stimuli transduction. Referring exclusively to previous, or historical, clinical practice may not be the only or best way to justify or take advantage of the therapeutic cascade of molecular events that descends from a savvy elicitation of wound healing [12].

Second, there is a great lack of standardization in the stimuli release, more clinical studies certainly is needed but also more basic science research is needed to guarantee robustness first, and appropriateness of dosage, i.e., effectiveness, then.

As an overall conclusion, it is to be expected that the rigorous and systematic exploration of these approaches open to a whole new area of medicine, which we call *Physicine*, with the potential to be *frugal* [53] both for the nature of some of the stimuli (mechanical in particular) and for the opening to biomedical *devices* repurposing, along the lines of *drug* repurposing, once dosages of stimulations can be released in well informed manners.

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