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Ultrasound combined with microbubbles modulates signal transduction pathways in blood cells

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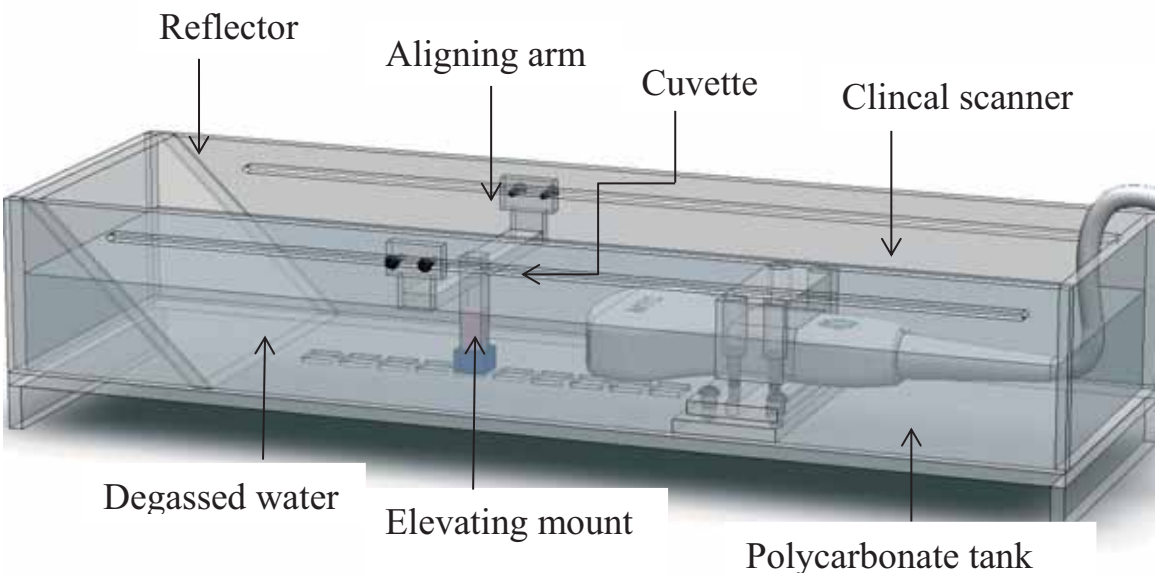
Ultrasound is widely used in medical diagnostics and is considered as a fast, cost-effective and safe imaging modality. Gas-filled microbubbles (MB) are introduced into the blood pool in order to enhance the signal-to-noise ratio in clinical contrast-enhanced ultrasonographical (CEUS) imaging [1]. CEUS is also explored for use in gene and drug delivery, by sonoporation [1]. Low-intensity pulsed ultrasound (LIPUS) is involved in activation of signaling pathways involved in cell stress [2], and is also shown to inhibit cancer cell proliferation and induce apoptosis in leukemia cells [3-7]. Limited is known about the signaling pathways simulated by ultrasound.
Intracellular signaling pathways in the monocytoid cell line MOLM-13 and peripheral blood mononuclear cells (PBMCs) were investigated after treatment with ultrasound alone or in combination with a gas-filled microbubble (MB). Three ultrasound intensities (mechanical index 0.16, 0.59, 0.72) for 10 minutes were employed with or without presence of microbubble contrast agent, using the set-up shown in figure 1. Multiparameter flow cytometry with protein modification specific antibodies was performed at predefined time-points ranging from 10 min and up to 24 hours after sonication to determine impact on intracellular signaling pathways.

Figure 1



MOLM-13 and PBMCs responded similarly to ultrasound and MBs, with phosphorylation of p38 and ERK1/2 MAPK with some cell specific differences.

Early induction of p38 MAPK signaling was seen in all cell types, but monocytes had a relative increase in phospho-p38 MAPK compared to MOLM-13, T lymphocyte, B lymphocyte and natural killer cells. Induction of phosphorylation of p38 MAPK was dependent on ultrasound intensities and MB presence. In general, increased phosphorylation of p38 MAPK is observed in response to stress stimuli and is involved in various cellular processes including differentiation and induction of cell death, acting upstream of the tumor suppressor p53 [8]. Futhermore, there is an example of downregulated p53 acetylation after increased phosphorylation of p38 MAPK [9], indicating involvement of an established stress pathway in ultrasound exposure.

Changes in phosphorylation of ERK1/2, AKT, NFκB and p53 as well as p53 acetylation were observed, but without alteration in total p53, clonogenicity or viability. It can be concluded that stress related signaling in leukocytes are affected by diagnostic ultrasound in vitro. The concerted upregulation of phosphorylated p38, ERK1/2 and AKT demonstrated in this study is previously described by other stress stimuli [10], suggesting involvement of a common mechanism.

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