

**Impact of extracellular substrate stiffness on macrophage activation**

Okamoto Takayuki, Haruki Usuda, Tanaka Tetsuya, Koichiro Wada

*Dept. Pharmacol., Fac. of Med., Shimane Univ.*

Increased tissue stiffness has been observed in aged vascular vessels and arteriosclerosis. Recent studies have revealed that substrate stiffness dictates macrophage activation and polarization. Thus, vascular stiffness has can potentially lead to macrophage activation that is at the center of the pathogenesis underlying chronic inflammatory diseases such as atherosclerosis. We have focused on the classical M1- and/or alternative M2-like macrophage activation on substrate whose stiffness values are relevant to normal vascular stiffness. Here we have studied the impact of the substrate stiffness on macrophage phenotypes.

In this study, we have utilized agarose gel for providing soft stiffness substrate and have found that soft substrate impairs pro-inflammatory activation of THP-1 cell under M1-promoting polarization condition. We have shown that soft substrate dictates the macrophage polarization to anti-inflammatory M2-like macrophage. Moreover, we have herein determined that peroxisome proliferator-activated receptor  $\gamma$  expression in macrophage on soft substrate contributes the anti-inflammatory macrophage activation.

The results shown in this study strongly suggest that extracellular substrate stiffness is a determinable factor for macrophage activation and polarization.