# Effects of Sex and 17 β-Estradiol on Cardiac Fibroblast Morphology and Signaling Activities In Vitro

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Several studies have demonstrated estrogen's cardioprotective abilities in decreasing the fibrotic response of cardiac fibroblasts (CFs) [1]. However, the majority of these studies are not sex-specific, and those at the cellular level utilize tissue culture plastic, a substrate with a much higher stiffness than physiological conditions. Understanding the intrinsic differences between male and female CFs under more physiologically "healthy" conditions will help to elucidate the divergences in their complex signaling networks. We aimed to do this by conducting a sex-disaggregated analysis of changes in cellular morphology and relative levels of profibrotic signaling proteins in CFs cultured on 8 kPa stiffness plates with and without 17 β-estradiol (E2). Cyclic immunofluorescent analysis indicated that there was a negligible change in cellular morphology due to sex and E2 treatment and that the differences between male and female CFs occur at a biochemical rather than structural level. Several proteins corresponding to profibrotic activity had various sex-specific responses with and without E2 treatment. Single-cell correlation analysis exhibited varied protein–protein interaction across experimental conditions. These findings demonstrate the need for further research into the dimorphisms of male and female CFs to develop better tailored sex-informed prevention and treatment interventions of cardiac fibrosis.

[1] Medzikovic et al., *J. Mol. Med.* (2019)