S46-2 Physiological roles of interactions between prostaglandin and chemokine signaling

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Timely interaction between the egg and sperm is required for successful fertilization. However, little is known about the signaling therein. Prostaglandin (PG) E receptor EP2-deficient (*Ptger2*$^{-/-}$) female mice exhibit a severe fertilization defect. Here we examined the molecular events leading to this failure. We found that expression of chemokines *ccl2*, *ccl7* and *ccl9* is induced in cumulus cells surrounding the egg after ovulation, and is augmented in *Ptger2*$^{-/-}$ cumuli. While these chemokines function to attract sperm to cumuli, the exogenous addition of these chemokines to wild type cumulus-egg complexes induces fertilization failure *in vitro*, and the addition of a CCL7 receptor antagonist improves fertilization rates in *Ptger2*$^{-/-}$ cumuli. Cumulus cells from *Ptger2*$^{-/-}$ mice, those from wild type mice pretreated with indomethacin, an inhibitor of PG biosynthesis, and those treated with CCL7 *in vitro* show RhoA-dependent cell contraction, and enhanced integrin expression and binding to the extracellular matrix (ECM) which confer these cumuli with resistance to hyaluronidase treatment and thus prevent sperm penetration. Hyaluronidase resistance of the ECM in these cumuli is relieved by the addition of EDTA or an RGD peptide. These results suggest that PGE_2-EP2 signaling negatively regulates chemokine-induced integrin engagement to the ECM and allows sperm penetration through cumulus matrices, and this interaction between PG and chemokine signaling is required for successful fertilization. We would like to discuss on physiological significance of such interactions in the maintenance of homeostasis.