Role of oocyte-secreted factors in prevention of cumulus cell apoptosis and enhancement of oocyte developmental competence

Tamer Hussein, MScMed

Research Centre for Reproductive Health,
Discipline of Obstetrics and Gynaecology,
School of Paediatrics and Reproductive Health,
University of Adelaide, Australia.

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Abstract

Paracrine factors secreted by the oocyte (oocyte-secreted factors, OSFs) regulate a broad range of cumulus cell functions. The capacity of oocytes to regulate their own microenvironment by OSFs may in turn contribute to oocyte developmental competence. The aim of this thesis was to examine whether cumulus cells exhibit a low incidence of apoptosis due to their close association with oocytes and their exposure to OSFs, and to investigate if OSFs have a direct influence on bovine oocyte developmental competence during in vitro maturation (IVM).

This thesis includes a series of studies designed to examine by various means the nature of the paracrine network of bone morphogenetic proteins (BMPs) and their binding proteins involved in the regulation of cumulus cell apoptosis. OSFs, in particular BMP-15 and BMP-6, but not growth differentiation factor 9 (GDF-9), reduced apoptosis of cumulus cells by following a gradient from the site of the oocytes. Morever, follistatin and a BMP6 neutralizing antibody, which antagonized the anti-apoptotic effects of BMP15 and BMP6, respectively, whether alone or combined, blocked ~50% of the anti-apoptotic actions of oocytes. These results demonstrated that OSFs, particularly BMP-15 and BMP-6, maintain the low incidence of apoptosis by establishing a localized gradient of bone morphogenetic proteins.

Results from the present thesis also demonstrated that OSFs enhance oocyte developmental competence during IVM, whether in their native form as an uncharacterized mix of growth factors secreted by the oocyte, throughout the oocyte

maturation period, or as exogenous BMP-15 and GDF-9, during the first 9 hour of IVM. Also, OSFs improved embryo quality as evident by increased blastocyst total and trophectoderm cell numbers. These results were further verified in neutralization experiments of the exogenous growth factors and of the native OSFs. Follistatin and the kinase inhibitor SB-431542, which antagonize BMP-15 and GDF-9, respectively, neutralized the stimulatory effects of the exogenous growth factors, and impaired the developmental competence of control cumulus-oocyte complexes (COCs).

The work presented in this thesis has provided multiple lines of evidence that OSF-regulation of the COC microenvironment is an important determinant of cumulus cell apoptosis and oocyte developmental programming.