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Role of PI3K/AKT/PTEN pathway inhibitors during IVM of mammalian oocytes: a systematic review

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Resumo

Modulation of phosphoinositide 3-kinase/protein kinase B/phosphatase and tensin homolog (PI3K/AKT/PTEN) pathway in mammals yields mixed results. Understanding its regulation can be a powerful tool for improving IVP. This systematic review aimed to map the evidence of mammalian PI3K/AKT/PTEN pathway modulation during IVM, to assess its effects on meiosis resumption/germinal vesicle breakdown (GVBD) and progression to metaphase II (MII), as well as its impacts on embryo development and quality. Three databases were fully searched, and 20 articles were considered suitable after screening. Ten, six, and four articles were reported in swine, bovine, and murine, respectively. A total of 48 IVM studies were identified considering different experimental conditions within the same article, among which 11 evaluated blastocyst yield in swine and bovine. Three PI3K inhibitors [3MA, Wortmannin (Wo), and LY294002 (LY)] and one AKT inhibitor (SH6) were investigated, accounting for 8, 29, 46, and 17% of the studies, respectively. The GVBD and MII rates were categorized as exhibiting positive effects (ability to inhibit) in 44% and 81% of the studies, respectively. In swine, 21 studies analyzed the supplementation of LY (52%), Wo (14%), 3MA (19%), and SH6 (14%) during IVM. Regarding GVBD, the addition of 5 x 10-6 to 7.5 x 10-5 M LY, 10-9 to 10-6 M Wo, and 10-2 M 3MA yielded a positive effect. Progression to MII was categorized as positive when 1 x 10-6 to 5 x 10-5 M LY, 10-5 M Wo, 10-2 M 3MA, or 5 x 10-5 M SH6 was added. In bovine, 17 studies analyzed the addition of LY (23%), Wo (65%), and SH6 (12%). The addition of LY (10-4 to 7.5x10-5 M) or Wo (10-8 to 10-6 M) was not able to inhibit GVBD, but a positive effect was shown in MII rate with 10-4 to 7.5 x 10-5 M LY, 10-8 to 10-6 M Wo, and 5 and 7.5 x 10-5 M SH6. In murine, 10 experiments were extracted in which 70 and 30% applied LY and SH6, respectively. Effects over GVBD and MII rates were positive, respectively, in 70% and 50% of the studies, and were dependent on media composition and pathway promoters, such as EGF and FSH. Post-IVM assessments were described in swine and bovine, and similar-to-control rates were seen. However, the addition of 2 x 10-8 M Wo in bovine was able to enhance cleavage and blastocyst rates. In this sense, two applied strategies allowed similar and greater than control rates: reduction of PI3K activity and temporary blockage of GVBD. Thus, GVBD and MII pathway regulation seems to depend on the species, inhibitor, concentration, and media supplementation. While in bovine, GVBD seems to be pathway independent, in swine and murine it is not well established. However, MII is highly controlled by the pathway on both bovine and swine. These data highlight the important roles of PI3K/AKT/PTEN pathway in mammals, the strategies, and the potential for improving IVP efficiency, underlining this pathway could be well explored in further studies.

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