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Leucine and Ovarian Resilience: A New Hope for Poor Responders in Fertility Treatments

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ABSTRACT

Leucine is one of the essential amino acids, and it plays a crucial role in the regulation of protein synthesis and cell growth through the mTOR (mammalian target of rapamycin) signalling pathway. Dysregulation of the mTOR pathway can be associated with various diseases, including cancer, diabetes, and neurodegenerative disorders. Correlating the mTOR signalling pathway and leucine with poor ovarian responders (POR) in the context of fertility and assisted reproductive technology (ART) involves understanding how this pathway might impact ovarian function and response to ovarian stimulation protocols. This review delves into the intricate interplay between the mammalian target of rapamycin (mTOR) pathway and fertility, with a particular focus on its implications for assisted reproductive technology.

Keywords: *Leucine, mTOR, poor responders, assisted reproductive technology.*

INTRODUCTION

Leucine is one of the essential amino acids, and it plays a crucial role in the regulation of protein synthesis and cell growth through the mTOR (mammalian target of rapamycin) signalling pathway. mTOR is a protein kinase that acts as a central regulator of cell growth, proliferation, and metabolism in response to various environmental cues, including nutrient availability.

Simplified overview of how leucine and the mTOR signalling mechanism work together:

1) **Leucine Sensing:** Leucine serves as a key nutrient signal in the mTOR pathway. When the concentration of leucine in the cell is sufficient, it triggers the activation of mTOR [1].

2) **mTOR Complexes:** mTOR exists in two main complexes: mTOR Complex 1 (mTORC1) and mTOR Complex 2 (mTORC2). In the context of leucine signaling, mTORC1 is the primary complex of interest [2].

3) **mTORC1 Activation:** Leucine activates mTORC1 by promoting its translocation to the lysosomal membrane, where it can interact with its activator, Rheb (Ras homolog enriched in brain). The exact mechanism of how leucine triggers this translocation is not fully understood but is thought to involve a series of intracellular signalling events [2].

4) **mTORC1 Signalling:** Once mTORC1 is activated, it phosphorylates various downstream targets, including the ribosomal protein S6 kinase (S6K) and the eukaryotic translation initiation factor 4E-binding protein (4E-BP1). Phosphorylation of these targets promotes protein synthesis and cell growth [2].

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5) **Protein Synthesis:** mTORC1 activation increases the translation of messenger RNA (mRNA) into proteins, particularly those involved in the regulation of cell growth and proliferation [3].

6) **Autophagy Inhibition:** mTORC1 activation also inhibits autophagy, a cellular process that degrades damaged organelles and proteins, promoting cellular quality control [3].

7) **Nutrient Sensing:** The mTOR pathway is not solely responsive to leucine but is part of a broader nutrient-sensing network. Other amino acids, growth factors, and energy status also play a role in regulating mTOR activity. It is important to note that the mTOR pathway is highly complex, and its regulation is influenced by many factors beyond leucine, including insulin, growth factors, and cellular energy levels (AMP-activated protein kinase, AMPK).[4] Dysregulation of the mTOR pathway can be associated with various diseases, including cancer, diabetes, and neurodegenerative disorders. Correlating the mTOR signalling pathway and leucine with poor ovarian responders (POR) in the context of fertility and assisted reproductive technology (ART) involves understanding how this pathway might impact ovarian function and response to ovarian stimulation protocols [4].

The correlation is as follows:

1) **Ovarian Function and Follicular Development**: In the context of female fertility, the ovaries are responsible for producing and releasing eggs (oocytes) during the menstrual cycle. Poor ovarian responders (POR) are individuals who have a reduced response to ovarian stimulation protocols used in in vitro fertilization (IVF) treatments. This reduced response often results in a lower number of oocytes available for retrieval [5].

2) **mTOR Signalling in Ovarian Function:** The mTOR signalling pathway, including mTORC1, is involved in various cellular processes, including the regulation of cell growth and proliferation. In the ovaries, mTOR signalling may also play a role in follicular development, oocyte maturation, and hormone production [6].

3) **Leucine and Ovarian Health:** Leucine, as a component of the mTOR signalling pathway, may have implications for ovarian health. Research has suggested that the mTOR pathway could be involved in regulating the growth and development of ovarian follicles. Leucine, as a nutrient signal, may influence the activation of mTOR in ovarian cells.

4) **Possible Connections to POR:**
   - **Reduced Oocyte Quality:** Dysregulation of the mTOR pathway or inadequate leucine signalling may affect the quality of oocytes produced in the ovaries. Poor oocyte quality can lead to POR.
   - **Response to Ovarian Stimulation:** Ovarian stimulation in IVF involves the use of medications to encourage multiple follicles to develop. If the mTOR pathway is not functioning optimally in the ovaries, it may affect the response to these stimulation protocols.
   - **Hormone Production**: mTOR signalling can influence the production of hormones in the ovaries. Dysregulation of hormone production may impact the ovarian response and the quality of eggs produced. It's important to note that the relationship between mTOR signalling, leucine, and POR is an area of ongoing research, and the specific

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mechanisms and clinical implications may not be fully understood. Factors contributing to POR can be multifactorial and include age, genetics, and underlying health conditions.

The correlation between the mTOR (mammalian target of rapamycin) pathway and the regulation of GDF9 (Growth Differentiation Factor 9) and BMP15 (Bone Morphogenetic Protein 15) in the context of ovarian function is an area of scientific interest and ongoing research. Understanding the potential interplay between the mTOR pathway and GDF9/BMP15 regulation have implications for fertility treatments and the development of novel therapies for reproductive disorders [7].

CONCLUSION

To conclude mTOR pathway, a pivotal signalling cascade governing cellular processes, has emerged as a subject of interest in reproductive biology. Existing research highlights its involvement in critical aspects of reproductive physiology, including oocyte development, folliculogenesis, and embryonic development. Furthermore, investigations into the modulation of the mTOR pathway, particularly using mTOR inhibitors like rapamycin, have been explored as potential strategies to enhance the success rates of ART procedures, such as in vitro fertilization (IVF).

Conflict of Interest – None to declare

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