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ABSTRACT TEMPLATE

Characterisation of the role played by the sperm factor, Phospholipase C zeta (PLCzeta), in mammalian cancer

Kashir, J[1,2]
[1] Department of Biology, College of Arts and Sciences, Khalifa University, Abu Dhabi, UAE
[2] Department of Comparative Medicine, King Faisal Specialist Hospital and Research Center, Riyadh, Kingdom of Saudi Arabia
junaid.kashir@ku.ac.ae

Background and Aim: Oocyte activation is a fundamental step in fertilisation, involving mitigation of cell cycle arrest and maternal mRNA recruitment, culminating in the initiation of embryogenesis in response to inositol 1,4,5-trisphosphate (IP3)-mediated changes in intracellular calcium (Ca2+) Numerous studies indicate that oocyte activation is mediated via a sperm-specific phospholipase C, termed PLCzeta (PLCζ), a ~74kDa protein in mouse (~70kDa in humans). Originally considered to be a testis/sperm-specific isoform of PLCs, recently indications suggest more than one isoform of PLCζ may be present within mammals, particularly within mice and humans. Indeed, NCBI indicates that there are multiple theorised isoforms of PLCζ. However, the presence and potential function of these isoforms are currently unidentified and unknown.

Methods: Quantitative reverse transcription PCR and immunoblotting of human and mouse tissue, and human patient cancer tissue.

Results: Data confirmed in both mouse and human a potential presence of non-testicular isoforms of PLCζ in the brain, and both male and female reproductive organs including the ovary, oviduct, placenta and uterus, and prostate, epididymis, and testes of both mice and human tissue. This has been observed at both RNA and protein levels using multiple primer sets and antibodies, respectively. More astoundingly, initial experiments suggest that PLCζ seems also to be significantly more abundant within tumor tissue compared to normal tissue, perhaps indicating a significant abundance of this enzyme in relation to abnormal Ca2+ signalling within cancer. Alterations in the activity and expression of the various isoforms of PLC have been detected in different human cancer types. Most data suggest that a PLC-mediated abnormality underlies a defective profile of Ca2+ release associated with such cancer cells and tissue. The profile of PLCζ within the tumor tissue compared to normal tissue is also intriguing as the dominant isoform in tumor tissue appears to be the functional isoform found in sperm (~70kDa), while in normal tissue this seems to be a separate and larger form (~100/140kDa). This is significantly intriguing as this would suggest a form of processing involved in PLCζ which has not yet currently been identified. Examination of PLCζ in these

scenarios would yield significant insight regarding pre- and post-activity processing, a key requirement for any enzymatic/proteomic understanding.

Conclusions: Collectively, these data represent an exciting new chapter in the analysis of PLCζ in non-testicular tissue, for the first time, indicating not only the potential presence of PLCζ, but also differential isoforms of PLCζ with potentially novel further roles. Furthermore, not only do our results indicate a novel paradigm for examination of PLCζ in non-testicular human tissue but could also represent a significant advance in our understanding of calcium signalling in cancer.