

Germ Cell specific Proteins can decide the fate of early embryonic or cancerous cells

Unique protein domains, concentration gradients, and asymmetric protein distributions or polarities are the principal forces establishing the identity of gametes and the fate of individual cells during early embryonic development. Here, I present our studies related to characterization of two novel representative regulatory proteins in the female germ cell, which play a key role during sperm-egg fusion and early embryonic development in mammals. I would also like to present our findings related to discovery of novel sperm cancer antigens, which has possible implications in development and formation of carcinoma cells.

The first protein which has been identified and characterized by our research group is a mammalian egg specific zinc endopeptidase consisting of 414 amino acids and characterized as a receptor in the microvillar domain of the oolemma of the mature oocyte for the Sperm acrosomal protein SLLP1 (which is important for fertilization); hence we named the newly identified as SAS1R (Sperm Acrosomal SLLP1 Receptor). SAS1R was found proteolytically active and highly regulated during oocyte maturation and early embryonic development. The protein appears to be important in sperm binding as well as in early embryonic development and belongs to a metalloprotease family possessing a specific zinc binding signature. Partial knock out mouse studies of SAS1R showed 36% reduction in the female fertility and this provides us an opportunity for designing a protease inhibitor based drug for inhibition of the protein, thus resulting in contraception. Further studies on the protein may also be helpful to unravel the highly coordinated molecular processes involved in sperm-egg cell fusion and conception.

The second protein, which has been characterized is a RNA binding protein consisting of 440 amino acids and has been named as Ecat1 (Embryonic stem cell associated transcript 1). Ecat1 was observed first in mouse mammalian oocyte cytoplasm in primary follicles and subsequently concentrated in the cortex of ovulated oocytes and to a restricted cortical cytoplasmic crescent in blastomeres of 2, 4 and 8 cell embryos. In morula, Ecat1 was observed to be concentrated at the apex of outer, polarized blastomeres and was undetectable in blastomeres of the inner cell mass. The Ecat1 pattern of morphogenetic distribution in early embryogenesis was similar to another RNA binding protein MOEP19 (Mouse Oocyte and Early Embryo Protein 19). Human orthologue of Ecat1 and HOEP19 (human orthologue of MOEP19) were also localized to a symmetrical cortical domain in human oocytes. Ecat1 and HOEP19 were found immediately adjacent on opposite strands of human chromosome 6 at q13 and supports existence of an oocyte pre-patterning locus at 6q13 in humans [and 9E1, 9D in mice] and a molecular mosaicism model of oocyte prepatterning. Recently, we also characterized Ecat1 as a biomarker for cancerous cells.

The third protein, which has been characterized is a sperm flagellar protein, named CABYR, which was originally cloned and characterized in human and mouse sperm cells and its mRNAs was abundantly expressed in the testis and selectively translated post-meiotically only in round spermatids. CABYR localized to the ribs and longitudinal columns

of the fibrous sheath in human sperm, where the protein is directly related to the glycolysis cascade. Preliminary evidences suggest that a few tumors revert to the gametogenic pathway and begin expressing CABYR proteins, a process which is normally restricted to only post-meiotic spermatids. The appearance of CABYR in tumor cells may also indicate a conversion from dependence on aerobic to anaerobic metabolism. We hypothesize that CABYR can be utilized as a unique biomarker for a subset of squamous cell carcinomas, and thus has potential to be used in diagnostic, prognostic, and treatment applications. Similarly another testis specific Phosphatase also has been characterized as a novel cancer biomarker.

Based on the above discoveries, it can be concluded that germ cells, cancerous cells and embryonic cells do share lot of proteins and pathways. However, each one of these cell type are unique and in the long term, an in-depth study on their interplay may be helpful to understand the basic process involved in development of these cell types and their regulations.