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Review

Intersecting roles of protein tyrosine kinase and calcium signaling during fertilization

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ABSTRACT

The oocyte is a highly specialized cell that must respond to fertilization with a preprogrammed series of signal transduction events that establish a block to polyspermy, trigger resumption of the cell cycle and execution of a developmental program. The fertilization-induced calcium transient is a key signal that initiates the process of oocyte activation and studies over the last several years have examined the signaling pathways that act upstream and downstream of this calcium transient. Protein tyrosine kinase signaling was found to be an important component of the upstream pathways that stimulated calcium release at fertilization in oocytes from animals that fertilize externally, but a similar pathway has not been found in mammals which fertilize internally. The following review will examine the diversity of signaling in oocytes from marine invertebrates, amphibians, fish and mammals in an attempt to understand the basis for the observed differences. In addition to the pathways upstream of the fertilization-induced calcium transient, recent studies are beginning to unravel the role of protein tyrosine kinase signaling downstream of the calcium transient. The PYK2 kinase was found to respond to fertilization in the zebrafish system and seems to represent a novel component of the response of the oocyte to fertilization. The potential impact of impaired PTK signaling in oocyte quality will also be discussed.

1. Introduction

Calcium signaling, in the form of the inositol triphosphate-induced release from internal stores, is a central aspect of the response of oocytes to fertilization in species as evolutionarily diverse as marine sponges and humans [1–3]. The scope of this signaling event is massive when considered at the cellular level involving the entire oocyte cytoplasm which ranges in diameter from 50 μm in the mouse to over a millimeter in amphibians. Fertilization drives an increase in intracellular free calcium from the resting level in the range of 10^{-7} M to a maximal amplitude in the 10^{-4} M range in marine invertebrates [4] and 10^{-6} M in mammalian oocytes [5]. Oocytes from marine invertebrates and fish respond to fertilization with a rapid 'cortical flash' due to opening of L-type channels in the plasma membrane allowing entry of calcium, followed by a high amplitude calcium transient mediated by inositol triphosphate (IP3) operated channels that begins in the immediate vicinity of the fertilizing sperm and spreads through the entire oocyte as a wave propagated across the entire oocyte [4,6]. In zebrafish, compartmentalization of the ooplasm into a central yolk mass and a thin layer of active cortical cytoplasm is reflected in the speed and amplitude of the high amplitude calcium transient. The calcium transient propagates rapidly through the cortical cytoplasm (9 μm/s) and more slowly with lower amplitude through the central yolk mass [7]. This pattern enables rapid induction of the cortical reaction and establishment of a block to polyspermy across these very large oocytes (700 μm) and more leisurely activation of metabolism in the central yolk mass. The pattern characteristic of marine invertebrates, amphibians, and fish differs from that in mammals where the calcium transient occurs as a series of oscillations that occur throughout the ooplasm. The detailed study by the Miyazaki laboratory [8] demonstrated that a fast calcium transient was initiated in the mouse oocyte at the site of sperm interaction within 1–4 min after the flagellum of the attached sperm ceased beating. The transient traversed the oocyte at a rate of 20 μm/s and accelerated as it progressed to the antipode. This first calcium transient exhibited a two step shape involving an initial 'shoulder' followed by a second, steeper rise that raised the possibility that different calcium channels or signaling mechanisms were involved at different stages of the transient as in marine invertebrates. The functional significance of this calcium transient is of tremendous importance to the individual since the very beginning of zygote development absolutely requires this signaling step [4]. The cytoplasmic machinery to support this signaling event is assembled during the process of oogenesis and arranged in final form during meiotic maturation

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[9,10]. In this way, the oocyte is highly specialized to respond to interaction with the fertilizing sperm with a rapid and decisive calcium signal that begins embryonic development.

The fertilization-induced calcium transient is interwoven with other signal transduction pathways which are arranged upstream and are thought to initiate, facilitate, and accelerate progression of calcium release in the oocyte. In turn, the calcium transient triggers a wave of downstream pathways critical to almost every aspect of egg activation [11]. Protein tyrosine kinases (PTKs), primarily from the SRC-family, have been recognized as important elements of the upstream pathways leading to the calcium transient in oocytes from species that fertilize externally [2]. However, these SRC-family protein tyrosine kinases (SFKs) play no essential upstream role in mammalian oocytes indicating that significant diversity exists in the pathways leading to the fertilization-induced calcium transient. The downstream pathways that respond to the fertilization-induced calcium transient appear to be essential for zygote development in all species studied to date and recent evidence has demonstrated that one or more PTKs may be an important component of these pathways as well [12,13].

Protein tyrosine kinases include multiple different families encompassing a wide variety of structural and functional variations that confer specific capabilities and signaling functions. PTKs share a tight specificity for tyrosine residues as the phosphate acceptor exhibiting a highly conserved catalytic domain [14]. PTKs are generally expressed in low quantities in cells relative to the more abundant serine-threonine protein kinases. However, within the PTK family, specific kinases are expressed at relatively high levels in certain cell types where they confer unique functional properties to that cell. Several PTKs that can function in calcium signaling cascades are expressed at relatively high levels in oocytes (Fig. 1) consistent with the central roles that calcium plays in the function of male and female gametes. The goal of the present review is to describe the array of PTKs that function as part of the upstream triggers for the fertilization-induced calcium transient or act downstream of this event to execute specific functions in the fertilized egg.

2. PTKs expressed in oocytes

The functional diversity between PTK families is based on their unique domain structure which provides many opportunities to confer specialized characteristics to a cell. In addition to the highly conserved catalytic domain, PTKs characteristically include specialized protein–protein interaction domains such as the SRC homology 2 (SH2) domain with strong binding specificity for

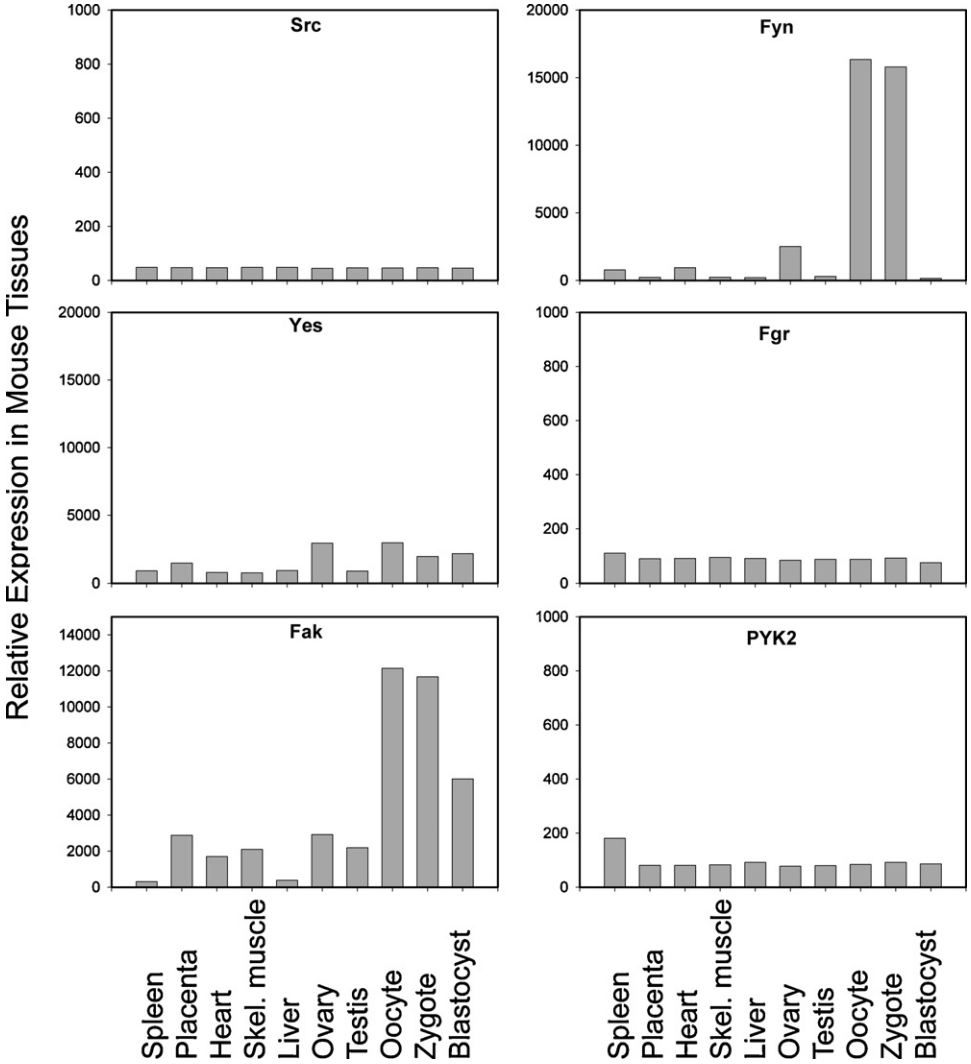

Fig. 1. Relative expression of PTKs in mouse tissues. Analysis of relative transcript abundance of selected SRC-family and FAK-family PTKs was retrieved from the mouse BioGPS expression array database (Novartis BioGPS, http://biogps.gnf.org [109]). Data for the *src*, *fyn*, *yes*, *fgr*, *fak, and PYK2* genes obtained from arrays representing oocytes, zygotes, ovary, and several additional tissues is presented along the horizontal axis (bottom).