ISSN 0025-7680

SYMPOSIUM

MEDICINA (Buenos Aires) 1999; 59: 546

GLYPICAN-3 IS A NOVEL INHIBITOR OF INSULIN-LIKE GROWTH FACTOR SIGNALING

JORGE FILMUS, HOWARD SONG, WEN SHI, ALFONSO DUENAS GONZALEZ, MITSUNORI KAYA AND DANIELLE CANO-GAUCI

Sunnybrook and Women's College Heath Sciences Centre and Department of Medical Biophysics, University of Toronto, Canada.

Glypicans are a family of heparan sulfate proteoglycans (HSPGs) that are linked to the cell surface through a glycosylphosphatidylinositol anchor. Our knowledge on the function of glypicans is still very limited, with most of the evidence suggesting that these molecules regulate the activity of various growth factors. It has also been proposed that glypicans are multi-functional molecules, with some of the functions being mediated by the sugar chains, and others by the core protein.

It has recently been reported that one member of the glypican family, glypican-3 (GPC3), is mutated in patients with the Simpson-Golabi-Behmel syndrome (SGBS). This is an X-linked syndrome characterized by overgrowth, and by several dysmorphisms that can include a distinct facial appearance, enlarged and dysplastic kidneys, vertebral and rib anomalies, syndactyly, heart defects, supernumerary nipples, and hernias. An increased risk for the development of pediatric tumors has also been reported. Death during infancy is very frequent, usually as a result of pulmonary infections.

The clinical features of SGBS suggest that GPC3 is a negative regulator of cell proliferation and apoptosis during development. Indeed, we have recently demonstrated that GPC3 can induce apoptosis or inhibit proliferation in a cell line specific manner.

Our laboratory has recently generated GPC3-knockout mice by homologous recombination. These mice exhibit several of the clinical features observed in SGBS patients, including developmental overgrowth, perinatal death, cystic and dysplastic kidneys, and abnormal lung development. In the particular case of the kidney we demonstrated that there is an early and persistent developmental abnormality of the ureteric bud/collecting system due to increased proliferation of cells in this tissue element.

SGBS is phenotypically very similar to the more extensively studied Beckwith-Wiedemann syndrome (BWS). Since biallelic expression of the paternally imprinted insulin-like growth factor-II (IGF-II) is thought to play a prominent role in BWS, it has been proposed that GPC3 is a negative regulator of this growth factor. We have recently generated experimental evidence supporting this hypothesis by showing that GPC3 can form a complex with the IGF receptor type I and inhibit its activation by IGF-II.

Since IGFs play an important role in the stimulation of proliferation and survival of malignant cells, it can be hypothesized that GPC3 can behave as an inhibitor of tumor growth. Indeed, our preliminary data show that GPC3 expression is downregulated in mesotheliomas and breast cancers, and that ectopic expression of this glypican in mesothelioma and breast cancer cell lines inhibits their proliferation or survival.