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The Role of Heat Shock Protein 90 in Human Reproduction

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Abstract: The aim of this study is to give a review of the current knowledge about the Heat shock protein 90 (Hsp90) and its relation with human reproduction. Hsp90 is a chaperone and conserved protein. It accounts for about 1-2% of total proteins. There are 2 isoforms of Hsp90: Hsp90α and β. The contribution of Hsp90 isoforms to various cellular processes including signal transduction, protein folding, protein degradation, cell survival and morphological evolution has gained high interest. The idea of considering infertility as an autoimmune disease is exciting. Various studies have demonstrated antiovary antibodies against Hsp90. In this study, such concepts and their implications have been reviewed.

Key words: Hsp90, chaperones, infertility, autoimmune disease, POI, POF

INTRODUCTION

Heat shock proteins are highly expressed cellular proteins in virtually all living organisms from bacteria to humans (Csermely *et al*., 1998). They function, as molecular chaperones are induced by heat shock and protect cells from heat stress. Heat shock proteins increase when the cells get exposed to elevated temperature (Crevel *et al*., 2001; Chen *et al*., 2006). Heat shock protein 90 (Hsp90) is one of the most common heat shock proteins. Hsp90 is a highly conserved cellular chaperon and one of the most abundant proteins in eukaryotic cells. It is in the order of 90 kDa in size.

The aim with this study is to give a review of the current knowledge about Hsp90 and its relation with human reproduction.

AN OVERVIEW OF HEAT SHOCK PROTEIN 90

Hsp90 has been estimated to account for about 1-2% of total cellular proteins and is involved in the stabilization and activation of >200 client proteins (Kaplan and Li, 2012). It has two major cytoplasmic isoforms which are constituted by gene duplication: The inducible Hsp90α and the constitutive Hsp90β form. The contribution of Hsp90 isoforms to various cellular processes including signal transduction, protein folding, protein degradation, cell survival and morphological evolution has extensively been studied (Csermely *et al*., 1998).

The most interesting aspect of Hsp90 is its structure in which it was identified the N-terminal domain which consists of a 2 layer α/β sandwich structure forming a pocket essential for ATP binding. The ability of Hsp90 to hydrolize and bind ATP determines its biological functions. There is also another segment in the structure of Hsp90, the middle segment which consists of a large αβα domain at the N-terminus of the construct connecting to a small αβα domain at the C terminus via a series of α-helices. This domain is considered the main site in which client proteins interact. The C-terminal domain in Hsp90 is essentially for dimerization and it is also a dimer of a small mixed α/β domain (Pearl and Prodromou, 2006). Numerous studies have explored the

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effects of Hsp90 inhibitors, these studies pointed to effective anti-inflammatory and anti-oxidative actions in vascular tissues (Lewis *et al*., 2000; Wax *et al*., 2003; Broemer *et al*., 2004; Murata *et al*., 2005; Hsu *et al*., 2007).

HSP90 AND INFERTILITY

Infertility has been associated with autoimmunity and various studies reported the development of the immune response against ovary (Luborsky, 2002; Forges *et al*., 2004). Autoimmunity of ovary has been reported among patients with Polycystic Ovarian Syndrome (PCOS), endometriosis and Primary Ovarian Insufficiency (POI) or Premature Ovarian Failures (POF) (De Moraes-Ruehsen and Jones, 1967; Luborsky, 2002). In a study by Barbarino-Monnier *et al*. (1991), it has been shown that women involved within *In vitro* Fertilization Embryo Transfer (IVF-ET) program to develop Antiovary Antibodies (AOA) that were associated significantly with poor reproductive outcomes. In their study, Coulam *et al*. (1981) pointed to the involvement of about 1% of all cases with POI by are known to autoimmunity. In another study, Coulam (1983) expressed his thoughts that other autoimmune diseases may coexist with POI, including systemic lupus erythematosus, Graves's and Addison's disease. According to studies by Wheatcroft *et al*. (1997) and Novosad *et al*. (2003) who reported that the detection of antiovary antibodies presented a challenge for scientists because antiovary antibodies were also detected among control groups. The problem has been more complicated due to lack of serum markers to confirm the diagnosis of ovarian insufficiency. A research group lead by Pires *et al*. (2006) was able to establish a simple and specific diagnostic test to detect AOA in women with infertility. According to studies of these research groups, they were able to show real antiovary antibodies in these women through the use of novel blocking approach and by thus they identified several new molecular and cellular targets (Pires *et al*., 2007). In another study by this group, they observed that the target antigens to range between 30-150 kDa among which was a 90 kDa protein to be the immunodominant antigen. Furthermore, the identity of the protein to be human Hsp90β (Pires and Khole, 2009). Several studies have shown the presence of anti-Hsp90 antibodies in the pathogenesis of several diseases including systemic lupus erythematosus, rheumatoid arthritis, osteocarcinoma and ovarian cancer (Faulds *et al*., 1995; Hayem *et al*., 1999; Trieb *et al*., 2000; Vidal *et al*., 2004).

In another study, concerning Premature Ovarian Failure (POF) which is defined, as the cessation of ovarian function after the onset of puberty and before the age of 40 years in women with hypergonadotropism (De Moraes-Ruehsen and Jones, 1967; Pires and Khole, 2009). POF has a group of classical causes including genetic, enzymatic, infectious or iatrogenic etiology (Kalantaridou *et al*., 1999; Chatterjee *et al*., 2007). The previous reasons are not always explaining all cases of POF in which they are diagnosed as idiopathic (Pires and Khole, 2009). In this group of POF patients, it has been shown that the ovarian autoimmunity and demonstrating of serum antiovary antibodies to be a phenomenon while detecting antiovary antibodies was considered a suitable marker for identification of the immunologic mechanisms involved in Autoimmune Premature Ovarian Failure (AI-POF) (Luborsky *et al*., 1990; Wheatcroft *et al*., 1994; Fenichel *et al*., 1997). Other researcher pointed to the potential of antiovary antibodies to be involved in other diseases including infertility and *In vitro* Fertilization and Embryo Transfer (IVF-ET) failures (Barbarino-Monnier *et al*., 1991; Gobert *et al*., 1992).

From an immunological point of view, the precise mechanisms beyond recognition of the ovarian antigens by the antibodies in sera are not well known. According to this context, it is crucial to identify and characterize target antigens to elucidate the associated immunologic mechanisms and also for setting up better means for the diagnosis and treatment of ovarian failure leading to infertility (Pires and Khole, 2009). Several autoantigens have reported against oocyte, corpus luteum, granulose cells and zona pellucida (Vallotton and Forbes, 1966; Sotsiou *et al*., 1980; Damewood *et al*., 1986; Koyama and Hasegawa, 2006). Furthermore, it has been demonstrated that the oocyte to be the most targeted cell by antiovary antibody among women with ovarian diseases poor Assisted Reproductive Technologies (ART) outcomes (Forges *et al*., 2004; Pires *et al*., 2007). Another source for autoantigens is the maternal antigen which is required by embryos (matter). This antigen has been identified in a mouse model for POF (Tong and Nelson, 1999) and in the sera of patients (Forges *et al*., 2004). In his study, Sundblad *et al*. (2006) reported another autoantigen, α enolase, as a target antigen in patients with Autoimmune POF (AI-POF). No data is known about its cell-specific immunolocalization.

CONCLUSION

In their study, Pires *et al*. (2007) showed that 30% of women with POF and 26% of women with IVF-ET groups were positive for antiovary antibodies using the Western blot methodology through the use of their novel blocking protocol. Further analysis demonstrated that Hsp90β, a 90-kd protein (EP90) to be the predominant antigenic target.

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