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Dipartimento di Medicina Molecolare e dello Sviluppo

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Scientific activity of my first year of PhD in Molecular Medicine, Academic year 2014/15

INTRODUCTION

Fertility is in general decreasing worldwide, with male infertility estimated to affect about 7% of men. The causes of this condition are often unknown, and about 40% of infertile men are oligozoospermic or azoospermic despite normal reproductive hormonal profile and a lack of other known causes of infertility.

Although several generations of researchers have investigated fertilization, this fundamental biological process remains poorly understood. Millions of genetically unique sperm cells must undertake the long journey to their destination deep inside the female genital tract.

To this end, spermatozoa are endowed with a distinct chemosensory ability to scan their environment and alter their spatial orientation. Chemotaxis of sperm is well documented for marine invertebrates with external fertilization, and it is also proposed to operate in sperm of mammals, including humans, to increase the likelihood of fertilization by chemically guiding spermatozoa to the mature oocyte within the oviduct.

However, there remains some controversy about receptor proteins that detect chemical compounds in the different fluids of the female reproductive tract and the chemoattractive cues that successfully guide the sperm towards the oocyte.

The chemical senses, i.e. smell and taste, are sensory modalities that generate aninternal representation of chemical information from the outside world. Olfactory receptors, conventionally

found on the ciliary membranes of nasal olfactory sensory neurons, have recently attracted much attention, due to their expression in the sperm flagella of different mammalian species. In addition, several studies have reported the expression of taste receptors and a signalling transduction cascade in non-taste tissues, including the digestive system, respiratory system urinary bladder, pancreas, liver, brain and testis.

Several studies have demonstrated, both in testis and in sperms, the expression of taste receptors and their signalling transduction cascade, highlighting their possible role in sperm maturation as well as in sperm behavior and fertilization by sensing chemicals in the milieu.

Numerous proteins, that serve as receptors for different food tastants, have been to date identified. Although ion channel are responsible for detecting salty and sour taste, sweet, bitter and umami tastes are detected by two families of G protein-coupled receptors (GPCR): T2Rs and T1Rs. A large family of TASR2 receptors mediate bitter gustatory signals. TAS1R receptor assemble into heterodimers: TAS1R2+ TAS1R3 forming a sweet receptor, and TAS1R1+TAS1R3 form an umami receptor. TAS1R taste receptors interact with specific Gα subunits, α-gustducin (Gαgust), encoded by the polymorphic gene GNAT3, and mediate gustatory signaling.

It has been reported that taste sensitivity varies greatly among individuals and that it is associated with single nucleotide polymorphisms (SNPs) in the taste receptor genes. The high frequency of human genetic variations of genes involved in taste perception results in a large variability from super-taster subjects to totally "non-taster" patients, in which inactivation of the receptor involved in signal transduction occurs.

METHODS AND MATERIALS

I have investigated the possible role of 14 selected SNPs in 11 genes so far identified with different types and degrees of male infertility. For this purpose 163 patients were enrolled at the Centre of Couple Sterility, Siena University Hospital (Italy), and were characterized for main sperm parameters, according to WHO (2010) guidelines: concentration, morphology, progressive and total motility and their DNA was isolated from buccal swab. All subjects were then genotyped for 14

single nucleotide polymorphisms (SNPs) in TAS2Rs/TAS1R and GNAT3 genes. The genotyping was performed using the KASPar SNP genotyping system. I also evaluated the presence and localization of α-gustducin and α-transducin in human ejaculated spermatozoa, in order to better understand the relationship between gustatory signaling and male infertility.

RESULTS

Preliminary data demonstrated a statistically significant association between sperm concentration and the TAS1R2 rs35874116 SNP and with the TAS2R49 rs7135018 SNP. Additionally, I observed a statistically significant association between total motility and the TAS2R14 rs11610105 variant. Indeed, G proteins α-gustducin and α-transducin are considered as specific markers of chemosensitive cells. My preliminary results clearly showed a faint α -gustducin and α-transducin signal in the equatorial segment and in the midpiece the tail, with a different intensity among individual sperm cell.

Abstracts, meeting attendance **and Training courses attended during first year of my PhD in Molecular Medicine:**

- **Genetic variability in bitter/sweet taste related genes and male infertility**

Piomboni P., Locci D., Campa D, Crifasi L., Capaldo A., Gori M., Luddi A. , Barale R.

- **Molecular biomarkers in cumulus and granulosa cells for oocyte quality estimation and pregnancy outcome prediction.**

Gori M., Luddi A., Crifasi L., Morgante G., Gambera L., Boschi L., Piomboni P. , De Leo V.

- XLVI Corso Permanente di Fisiopatologia della Riproduzione Umana e Tecnologie della Riproduzione Assistita - APPROFONDIMENTI E DIBATTITI IN FISIOPATOLOGIA DELLA RIPRODUZIONE, 24-27 November 2015

- I° Congresso congiunto SIA-SIERR- IL MASCHIO E L'ETEROLOGA: dallo spermiogramma ai recuperi chirurgici ed alla crioconservazione, 18 April 2015

- NOVITÀ PER LA PCOS – SIPO, 15 May 2015

- 31st Annual Meeting of the European Society of Human Reproduction and Embryology (ESHRE), 14-17 June 2015

- Stress, Inflammation and Reproduction - IBSA FOUNDATION, 3 July 2015

- START UP AND TECHNOLOGY TRANSFER CFU n. 2, 15-17 September 2015

- SISTEMI DI RICERCA EUROPEI: PROJECT DESIGN E GESTIONE DEI PROGETTI DI RICERCA CFU n.215-17, September 2015

- Internships at the Department of Biology, Genetics Unit, Pisa University, Pisa , Italy