专栏·中国卓越国际论文

匡延平·研究组

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首次发现人类全新遗传病——卵子死亡，并明确致病基因 *PANX1*

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上海交通大学医学院附属第九人民医院辅助生殖科匡延平研究组首次发现一种全新的遗传疾病，命名为“卵子死亡”，并就疾病的致病基因及作用机制进行挖掘。该研究成果以 *A pannexin 1 channelopathy causes human oocyte death* 为题于 2019 年 3 月发表于国际著名学术期刊 *Sci Transl Med*。复旦大学博士研究生张治华、西北妇女儿童医院师娟子教授、复旦大学附属妇产科医院孙晓溪教授、上海交通大学医学院附属第九人民医院辅助生殖科李斌博士和闫铮博士为论文的共同第一作者，上海交通大学医学院附属第九人民医院匡延平教授、复旦大学生命科学学院桑庆副研究员和生物医学研究院王磊教授为论文的共同通信作者。上海交通大学医学院和复旦大学为论文的共同通信单位。

早在 2003 年，匡延平教授于临床试管婴儿治疗过程中发现了一例奇特的患者。该患者的卵子形态及体外受精过程均正常，但受精第 2 日后所有胚胎均出现发黑、萎缩、退化的现象。其后，匡延平教授又陆续发现了 1 例具有相似表型的家族性患者及 1 例具有更严重表型的散发患者，该 2 例患者在卵子取出后未受精时即表现为发黑、萎缩、退化，而究竟是由何种原因及机制导致则完全未知。2015 年，上海交通大学医学院附属第九人民医院匡延平研究组联合复旦大学王磊研究组将此疾病命名为“卵子死亡”并开展相关研究。通过 3 年多的攻关，该联合研究组在 4 个独立家系中发现 *PANX1* 基因存在不同的突变且该疾病符合孟德尔显性遗传特点，继而明确卵子死亡是一种新的孟德尔遗传病。

PANX1 为糖基化蛋白 Pannnexin（PANX）家族成员之一。联合研究组通过在细胞及卵子中开展的功能实验发现，*PANX1* 基因的突变会改变 PANX1 的糖基化模式，且与卵子死亡的发生密切相关。该联合研究组通过体外实验进一步研究发现，突变不仅可以引起 PANX1 通道的异常激活，还可加速卵子内部 ATP 的释放，继而导致卵子死亡。随后，联合研究组制作了在卵子中特异性过表达突变型 *PANX1* 的鼠模型，结果显示：突变鼠模型表现为不孕并能准确模拟出卵子死亡的表型。因此，该项研究成果揭示了 *PANX1* 突变的致病机制，发现了人类新的孟德尔遗传病、糖基化疾病及离子通道疾病——卵子死亡；同时，也为后续相关研究提供了首个 *PANX1* 病理学功能的鼠模型。

该项目由上海交通大学医学院和复旦大学的科研人员合作完成。匡延平研究组长期致力于人类配子及早期胚胎发育异常的分子机制研究，此次研究的发现是在人类早期生殖异常的遗传学基础研究方面取得的又一原创性成果，为辅助生殖中的精准医学实践奠定了基础。该项目也得到了国家自然科学基金面上项目的支持。

A pannexin 1 channelopathy causes human oocyte death

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Abstract:

Connexins and pannexins are two protein families that play an important role in cellular communication. Pannexin 1 (PANX1), one of the members of pannexin family, is a channel protein. It is glycosylated and forms three species, GLY0, GLY1, and GLY2. Here, we describe four independent families in which mutations in *PANX1* cause familial or sporadic female infertility *via* a phenotype that we term “oocyte death.” The mutations, which are associated with oocyte death, alter the PANX1 glycosylation pattern, influence the subcellular localization of PANX1 in cultured cells, and result in aberrant PANX1 channel activity, ATP release in oocytes, and mutant PANX1 GLY1. Overexpression of a patient-derived mutation in mice causes infertility, recapitulating the human oocyte death phenotype. Our findings demonstrate the critical role of PANX1 in human oocyte development, provide a genetic explanation for a subtype of infertility, and suggest a potential target for therapeutic intervention for this disease.

学者介绍

匡延平 博士

主任医师、博士生导师

ORCID ID：0000-0003-2985-5793

KUANG Yan-ping M.D

Chief Physician, Doctoral Supervisor

ORCID ID: 0000-0003-2985-5793

匡延平（1964—），上海交通大学医学院附属第九人民医院辅助生殖科主任。1993 年于复旦大学上海医学院（原上海医科大学）获妇产科专业博士学位。1997—1998 年赴澳大利亚 Adlaide 大学做访问学者。1998 年开始从事辅助生殖技术临床工作。2003 年创立上海交通大学医学院附属第九人民医院辅助生殖科。现任中国康复医学会生殖健康专业委员会主任委员、中国医学促进会生殖医学分会副主任委员、中国医师协会生殖医学专业委员会常务委员、上海市中西医结合学会生殖医学分会副主任委员。

长期致力于生殖内分泌和生殖遗传疾病领域的研究。20 余年来，完成不孕症诊治 80 000 余例，治愈患者数万人。在辅助生殖领域，其重要成就之一即为发明了多种新的促排卵方法。其中，2013 年开创的微刺激后行二次刺激的方法被国际同行冠名为“上海方法”（Shanghai protocol），成为首个以中国城市命名的该领域医疗技术；2015 年，由其创建的全新超排卵方法——高孕激素状态促排卵（progestin-primed ovarian stimulation，PPOS）成为了控制排卵技术研究的里程碑式进展。上述研究成果均被国际高影响力杂志 *Hum Reprod Update* 报道并给予高度评价。在生殖遗传疾病研究方面，陆续发现卵子成熟障碍、卵子受精障碍、卵子死亡等疾病的分子遗传机制，并于 *N Engl J Med*（2016）、*Am J Hum Genet*（2017，2018）、*Sci Transl Med*（2019）等发表相关成果。近 5 年，以第一作者或通信作者发表 SCI 论文 50 余篇。先后主持科技部重点专项“生殖健康及重大出生缺陷防控研究”1 项，国家自然科学基金 3 项以及上海市自然科学基金若干。申请专利 5 项。2017 年获全国妇幼健康科学技术奖一等奖。

KUANG Yan-ping (1964—), director of Assisted Reproduction Department of Shanghai Ninth People′s Hospital, Shanghai Jiao Tong University School of Medicine. He got his Doctor′s degree of obstetrics and gynecology from Shanghai Medical College of Fudan University in 1993. From 1997 to 1998, he was a visiting scholar at Adlaide University, Australia. Then, Dr.

KUANG began to study assisted reproductive technology in 1998, and established the Assisted Reproduction Department of Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine in 2003. Currently, he is the chairman of Reproductive Health Professional Committee of Chinese Association of Rehabilitation Medicine, the vice chairman of Reproductive Medicine of China Science and Technology Industry Association, the standing committee of Reproductive Medicine Professional Committee of Chinese Medical Doctor Association, and the vice chairman of Reproductive Medicine of Shanghai Association of Chinese Integrative Medicine.

Dr. KUANG's researches mainly focus on the field of reproductive endocrine and reproductive genetic diseases. Over 20 years, more than 80 000 cases of infertility have been diagnosed and treated, and tens of thousands of patients have been cured. One of his outstanding achievements in the field of assisted reproduction technology is the innovation of new superovulation methods. In 2013, he innovated the method of double stimulation named "Shanghai protocol" by international counterparts, which is the first medical technology named as Chinese city in this field. In 2015, he originally invented another important ovulation induction method named progestin-primed ovarian stimulation (PPOS), which is a landmark progress in controlled superovulation technology. The achievements have been reported by *Hum Reprod Update* with high evaluation. In addition, Dr. KUANG's researches also focus on molecular mechanisms of reproductive genetic diseases, such as oocyte maturation arrest, fertilization failure and oocyte death. Related articles have been published in *N Engl J Med* (2016), *Am J Hum Genet* (2017, 2018), and *Sci Transl Med* (2019). In the past five years, he has published more than 50 SCI-indexed papers as the first author or corresponding author. He hosted one grant of Key Projects of the Ministry of Science and Technology of China, three grants of National Natural Science Foundation of China, and several grants of Natural Science Foundation of Shanghai. Also, he has applied for five patents. In 2017, he won the first prize of National Health Maternal and Child Science and Technology Award.

上海交通大学医学院附属第九人民医院辅助生殖科

上海交通大学医学院附属第九人民医院辅助生殖科成立于 2003 年，经过 16 年的发展已逐渐成为了一支强大的学科团队，包括临床医师、胚胎学家及科研人员。目前，该科室累计完成临床取卵超过 80 000 周期，成为上海市取卵周期总量最多的辅助生殖医疗机构，其临床妊娠结果也处于全国前列。目前，辅助生殖科已开展 PPOS 方案临床和机制研究、胚胎发育研究、生殖遗传研究以及线粒体遗传病阻断治疗研究等，并取得了一系列原创性重要成果。

The Assisted Reproduction Department of Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine was established in 2003. After 16 years of development, a strong team of clinical doctors, embryologists and scientific researchers has been gradually established. At present, more than 80 000 cycles of oocytes retrieval have been completed, which is the largest number among the assisted reproductive medical institutions in Shanghai with the leading clinical pregnancy results in China. At present, the Assisted Reproduction Department has carried out clinical and mechanism study of PPOS protocol, embryonic development research, reproductive genetic research and mitochondrial inheritance disease blocking treatment research, and has achieved a series of original important discoveries.

5 篇代表性论文：

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