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Expressão de marcadores moleculares em espermatogônias

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RESUMO

GIASSETTI, M. I. **Expressão de marcadores moleculares em espermatogônias**. [Expression of molecular markers in spermatogonia]. 2015. 163 f. Tese (Doutorado em Ciências) – Faculdade de Medicina Veterinária e Zootecnia, Universidade de São Paulo, São Paulo, 2015. Tese (Doutorado em Ciências) - Faculdade de Veterinária, Universidade de Zaragoza, Zaragoza, 2015.

Em mamíferos, a espermatogênese é mantida pela autorrenovação e diferenciação das células-tronco espermatogoniais (SSC). Apesar da grande importância do SSC para a fertilidade masculina, em *Bos taurus* pouco se sabe sobre a sua identificação e biologia celular. Para roedores, mais de 30 marcadores para células germinativas indiferenciadas já foram descritos. No entanto, ainda não é conhecido um marcador específico apenas para SSC. Quase todos são também expressos por gonócitos, espermatogônias mais diferenciadas ou mesmo células somáticas. *Yin Yang 2* (YY2) é um factor de transcrição expresso nas células com a morfologia de gonócitos e SSC, sendo um candidato a marcador de SSC. Assim, a identificação de novos marcadores para SSC e factores que afectam a sua expressão, tais como a idade, são fundamentais para o desenvolvimento da biotecnologia como transgenia e tratamento de infertilidade, nos quais as SSC poderiam ser ferramentas biológicas importantes. Assim, nesta tese temos duas hipóteses principais: 1) a idade do dador afeta a expressão de marcadores moleculares específicos de SSC bovinas assim como potencial de células-tronco dessas células e que as sequências de DNA em que se associa YY2 regulam a expressão génica de SSC em camundongos. Os objetivos específicos, organizados em 4 artigos científicos, foram: identificar a melhor plaqueamento diferencial para enriquecer SSC bovina (artigo 1), verificar se a expressão de marcadores moleculares de SSC bovina difere entre adultos pré-púberes (artigo 2 e 3), identificar novos marcadores específicos para SSC em *Bos taurus* (artigo 3), verificar que a idade afeta o potencial de célula-tronco de SSC bovinas (artigo 3), descrever YY2 como um marcador específico para SSC em camundongos e verificar se as sequências DNA associadas YY2 são *loci* de importância para SSC. Assim, definimos o melhor plaqueamento diferencial para o enriquecimento de SSC bovinas, que idade afeta a expressão marcadores já estabelecidos assim como genes específicos do transcriptoma de SSC bovinas e que idade também afeta o seu potencial de células-tronco (ensaio de repopulação).

Concluimos também que YY2 é um marcador para SSC de camundongo em cultivo, em animais adultos e que as sequências do genoma que se associam YY2 possivelmente tem capacidade de regulação génica em SSC murina.

Palavras-chave: SSC. Célula germinativa indiferenciada. Marcadores moleculares. Idade. Yin Yang 2.

RESUMEN

GIASSETTI, M. I. **Expresión de marcadores moleculares en espermatogonias**. [Expression of molecular markers in spermatogonia]. 2015. 163 f. Tese (Doutorado em Ciências) – Faculdade de Medicina Veterinária e Zootecnia, Universidade de São Paulo, São Paulo, 2015. Tese (Doutorado em Ciências) - Faculdade de Veterinária, Universidade de Zaragoza, Zaragoza, 2015.

En mamíferos la espermatogénesis es mantenida por la auto-renovación y diferenciación de las células madre espermatogoniales (SSC). A pesar de la gran importancia de las SSC para la fertilidad masculina, en *Bos taurus* poco se sabe acerca de su identificación y biología celular. En ratones se han descrito más de 30 marcadores para células germinativas indeferenciadas pero todavía no se ha descrito un marcador específico para SSC. Casi todos marcadores de SSC son también expresados por gonocitos, espermatogonias más diferenciadas o hasta células somáticas. *Yin Yang 2* (YY2) es un factor de transcripción que se expresa en células con la morfología y la localización propia de gonocitos y SSC, siendo un candidato a marcador para SSC. La identificación de nuevos marcadores para SSC y de factores que afectan su expresión, como la edad, son fundamentales para el desarrollo de biotécnicas en que se puedan utilizar las SSCs como herramientas biológicas en transgenesis animal y tratamiento de infertilidad. Este trabajo tiene dos hipótesis principales: 1) la edad del bovino donante afecta la expresión de marcadores moleculares específicos de las SSC así como su potencial de célula madre y 2) que YY2 tiene funciones importantes en SSC, y que las secuencias genómicas a las que se asocia YY2 representan *loci* de importancia para SSC. Los objetivos específicos fueron organizados en cuatro artículos científicos: identificar el mejor plaqueamiento diferencial para enriquecer SSC bovinas (artículo 1), comprobar que la expresión de marcadores moleculares de las SSC bovinas difiere entre animales prepúberes y adultos (artículo 2 y 3), identificar nuevos marcadores específicos para SSC de *Bos taurus* (artículo 2 y 3), comprobar que la edad afecta el potencial de célula madre de las SSC bovinas (artículo 3), describir YY2 como un marcador específico para SSC en ratón y testar si las secuencias de DNA a las que se asocia YY2 (identificados previamente) tienen capacidad de regulación génica en SSC. Como conclusiones, definimos el mejor plaqueamiento diferencial para el enriquecimiento de SSC bovinas, aportamos pruebas que la edad afecta la

expresión de marcadores ya consagrados, afecta un número pequeño la expresión de un número restringido de genes dentro del transcriptoma de SSC bovino, y comprobamos que la edad también afecta su potencial de célula madre (ensayo de repoblación). Aportamos a la identificación de YY2 como marcador de SSC en cultivo, de ratones adultos, y demostramos la capacidad de regulación genética en SSC de ratón de las secuencias a las que se asocia YY2.

Palabras clave: SSC. Células germinales indiferenciadas. Marcadores moleculares. Edad. Yin Yang 2.

ABSTRACT

GIASSETTI, M I. **Expression of molecular markers in spermatogonia**. 2015. 163 f. Tese (Doutorado em Ciências) – Faculdade de Medicina Veterinária e Zootecnia, Universidade de São Paulo, São Paulo, 2015. Tese (Doutorado em Ciências) - Faculdade de Veterinária, Universidade de Zaragoza, Zaragoza, 2015.

Mammalian spermatogenesis is sustained by self-renewal and differentiation of spermatogonial stem cells (SSC). Despite the importance of the SSC for male fertility, in *Bos taurus* little is known about their identification identity and cell biology. For rodents, more than thirty markers for undifferentiated germ cells have already been described. However, none of these represents a marker specific for SSC, as most are also expressed in gonocytes, differentiated spermatogonia or even somatic cells. *Yin Yang 2* (YY2) is a transcription factor specifically expressed in cells with the morphology of gonocytes and SSC in the mouse, being a candidate marker for SSC. For the use of SSC as an important biological tool in the development of biotechnology such as transgenesis and the treatment of infertility, it is important to identify new markers for SSC and factors that affect their expression, such as the age of donors. Therefore, the experimental work described in this thesis was based on two main hypothesis: (1) the donor age affects the expression of specific molecular markers in SSC as well their potential as stem cells and 2) YY2 exerts important functions in SSC and genomic targets correspond to *loci* relevant for gene regulation or genome management in SSC. The specific goals have been organized in 4 manuscripts as follows: optimization of differential plating to enrich for bovine SSC (Article 1), check if the expression of molecular markers of bovine SSCs differs between prepubertal and adult donors (Article 2 and 3), identify new markers specific for SSC in *Bos taurus* (Article 3), continuation of the initial description of YY2 as a specific marker for SSC in mice and check if sequences bound by YY2 *in vivo* harbor the capacity to influence gene expression in SSC. As conclusions, we present an optimized differential plating protocol for the enrichment of bovine SSC, we conclude that age effects the expression of SSC markers, the expression of specific genes of bovine SSC and that age also affects their potential as stem cells (measured in repopulation assays). We also contribute to the description of the restricted expression of YY2 in prepubertal and adult SSC in mice and we show that YY2 binding sites represent genomic sequences relevant for control of gene expression.

Keywords: SSC. Undifferentiated germ cells. Molecular markers. Age. Yin Yang

1 INTRODUCTION

Spermatogenesis is a classical and complex biological stem cell-dependent process. In a correct environment, called the testicular niche, few spermatogonial stem cells (SSC) maintain the undifferentiated cell pool by self-renewal and some committed cells differentiate to the spermatic cell line. In domestic animals, SSC characterization and properties are not as elucidated as in rodents. In adult mice testis, SSC are a rare cell type (TEGELENBOSCH; DE ROOIJ, 1993); however, for the percentage of SSCs in adult testis is not clear in domestic animals. The development of biotechnological tools to identify unique properties of SSC and to purify those cells with high efficiency is fundamental to better understand SSC molecular biology and to apply SSC in animal transgenesis or infertility treatment.

Until recently, the highest rate of purified SSC was described in mice (BELLVÉ et al., 1977), which also is the species with highest number of specific markers described for undifferentiated spermatogonia (MEINHARDT et al., 1998; PHILLIPS; GASSEI; ORWING, 2010; ZHENG et al., 2014). More than thirty specific markers for mice spermatogonia were described (PHILLIPS; GASSEI; ORWING, 2010) such as ITGA6 (SHINOHARA et al., 1999), OCT4 (GUAN et al., 2009), GFRA1 (MENG et al., 2000), THY1 (KUBOTA; AVARBOCK; BRINSTER, 2003), CD9 (KANATSU-SHINOHARA; TOYOKUNI; SHINOHARA, 2004), PLZF (BUAAS et al., 2004) and CXCR4 (YANG et al., 2013). Yin Yang 2 (YY2) is a DNA-binding transcription factor that expression was reported in almost all cell types, tissues and embryo developmental stages but YY2 expression is not ubiquitous (LUO, J. et al., 2006; CHENG et al., 2008). Recently, high expression of YY2 was observed in undifferentiated mice spermatogonia in vivo and in vitro, indicating that YY2 might be a new candidate marker for undifferentiated spermatogonia in mice (PEREZ-PALACIOS et al., 2014¹).

New candidates for SSC molecular markers have been proposed for mice, but transposition of knowledge from mice to domestic animals have some limitations in replicability of methods to enrich SSC, to understand self-renewal pathways and to

¹ PEREZ-PALACIOS, R.; GIASSETTI, M. I.; ACÍN, C.; CLIMENT, M.; GUALLAR, D.; MUNIESA, P.; SCHOORLEMMER, J. On a possible role for YY2 in male germline, [2014]. Data not published.

obtain long-term cell culture (HE et al., 2015). Such as in other domestic animals, only few specific markers for undifferentiated spermatogonia were described in cattle: THY1 (REDING et al., 2010), PLZF (REDING et al., 2010), UCHL1 (GOEL et al., 2010), NANOG, POU5F1, VASA (FUJIHARA et al., 2011), DBA affinity (IZADYAR et al., 2002) and CXCR4 (GOISSIS et al., 2015²).

Adult stem cells support tissues and organs maintenance and homeostasis, but tissue regeneration dramatically decrease with age (BOYLE et al., 2007). The age effect on SSCs functionality and properties are not complete clear for mouse and other mammalian species (JOHNSON et al., 1991; KOKKINAKI et al., 2010; FUJIHARA et al., 2011). In flies, the total number of germline stem cells, germline stem cell division and self-renewal factors decrease with aging (BOYLE et al., 2007; CHENG et al., 2008). In mice, SSC transcriptome is affected by age and consequently, by sexual maturation (KOKKINAKI et al., 2010). In livestock, offspring genetic gain is highly correlated with the male ancestor which most of times is a breeding adult male with previously approved genetic merit. However, the effects of sexual maturation in stem germ cells are unclear in mammals with long prepubertal phase, such as the bovine.

The present doctoral thesis goal is to study the expression of new and previously described specific spermatogonial markers for bovine and mice. We are also interested to understand the effect of age/sexual maturation in the expression of markers and stem cell functionality of bovine SSC. For better understanding, the objectives and results of this study were divided into four chapters organized as scientific articles. In chapter 1 (Comparison of spermatogonial stem cell markers after diverse differential plating methods of bovine testicular cells), we proposed to evaluate three differential plating methods to enrich spermatogonia based on the expression of interspecific molecular markers ITGA6, GFRA1, CXCR4 and THY1. In chapter 2 (Effect of age on expression of spermatogonial markers in bovine testis and isolated cells), we aimed to evaluate effect of age on the expression of undifferentiated spermatogonial markers in testis and in enriched testicular cells from prepubertal calves and adult bulls. Chapter 3 (Comparison of molecular and functional elements of CXCR4⁺ germ cells in pre-pubertal and adult bulls) we aimed

² GOISSIS, M. D.; GIASSETTI, M. I.; WORST, R. A.; MENDES, C. M.; MOREIRA, P. V.; ASSUMPÇÃO, M. E. O. A.; VISINTIN, J. A. Spermatogonial stem cell potential of CXCR4-positive cells from prepubertal bovine testis, [2015]. Data not published.

to verify if sexual maturation affect CXCR4+ germ cell function and gene expression. In chapter 4 (Selected YY2 binding sites positively mediate transcriptional activity in Spermatogonial Stem cells) we aimed to clarify questions regarding the expression of YY2 in postpuberal mouse testis, regarding the intracellular localization of YY2 in SSC and verify YY2 and REX1 binding sequences ability to influence gene expression and transcriptional control at a distance.

8 CONCLUSIONS

Based on the presented data, this study has two main conclusions matching with our principal hypothesis. The first principal conclusion is: age/sexual maturity affects stem cell potential of bovine undifferentiated germ cells, as observed in the specific expression of SSC molecular markers and genes associated with SSC cellular biology. Specifically, we observed that differential plating is an effective technique to enrichment of undifferentiated spermatogonial stem cell being more efficient when performed without laminin coating (article 1), age/sexual maturity affects expression of consecrated undifferentiated spermatogonia molecular markers for bovine such as *UCHL1* (article 2) and age/sexual maturity affects expression of specific genes (*SELP* and *UCHL1*) (article 2). We also observed, that *CXCR4* is a specific molecular marker for SSC and its expression is conserved in SSC provided from prepubertal calves and adult bulls (article 3). However, age/sexual maturity affects expression of specific genes (*THY1* and *LIMS2*) and the stem cell potential of bovine *CXCR4*⁺ SSC (article 3).

The second main conclusion of present study is: *YY2* is a specific molecular marker for postpubertal mice SSC (article 4) and possibly *YY2* could be considered as interspecific candidate gene for SSC. Complementing that conclusion, we observed that *YY2* binding sequences possibly influence gene expression and transcriptional control at a distance in SSC (article 4). Moreover, *REX1* binding sequences also possibly control gene expression in embryonic stem cells (article 4).

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