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Review Article

# Stem cells and uterine leiomyomas: What is the evidence?

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## ABSTRACT

Uterine leiomyomas, also known as uterine fibroids or uterine myomas, are the most common benign gynecologic tumors found in women of reproductive age. In spite of the numerous published studies evaluating the hormonal dependency, epidemiology, molecular biology, pathology, and genetics of leiomyomas, many questions remain unanswered. The remodeling of the uterus in response to hormonal stimuli and its return to a basal state may be related to adult stem/progenitor cells residing in the endometrial and myometrial layers. Recent published papers on stem cells and their paracrine interactions with more specialized cell populations within leiomyomas may help establish the missing link between the development of treatments designed to stop the growth of leiomyomas and therapies devised to eliminate them. Therefore, this study aimed to address the current paradigm regarding the evidence available on the role of stem/progenitor cells in the pathogenesis of uterine leiomyoma. Only a handful of studies involving humans have been published to date describing the presence of somatic stem cells (SSCs) in the myometrium and leiomyomas. No solid conclusion has been established thus far. Despite the fact that these studies strongly pointed to the vital role human leiomyoma stem cells might play in initiating the development of myomas, huge gaps still persist in the literature. Studies to identify putative myometrial and leiomyoma-specific markers might offer new possibilities for understanding the origin of these tumors and perhaps help develop new nonsurgical noninvasive treatments.

**Keywords:** Leiomyoma, fibroid, myoma, stem cells

## INTRODUCTION

Uterine leiomyomas, also known as uterine fibroids or uterine myomas, are the most common gynecologic tumors found in women of reproductive age. Although benign, these tumors may be responsible for reproductive and gynecologic disorders ranging from infertility and pregnancy loss to pelvic pain and abnormal uterine bleeding, in addition to possibly accounting for 200,000 hysterectomies every year in the US alone (Parker, 2007; Bulun, 2013; Doherty *et al*., 2014)

Despite the numerous published studies evaluating the hormonal dependency, epidemiology, molecular biology, pathology, and genetics of fibroids, many questions concerning the etiology and the role of genetic or environmental factors on their pathogenesis remain unanswered (Flake et al., 2003; Sozen & Arici, 2006; Blake, 2007; Ciarmela *et al*., 2011). Although the precise etiology and pathogenesis of myomas are unknown, advances have been made in understanding hormonal, genetic and growth factors, and the molecular biology of these benign tumors (Segars *et al*., 2014; Talylor *et al*., 2014).

The uterus displays fantastic plasticity in terms of tissue remodeling in mammals. It comprises the endometrium and an outer smooth muscle layer called myometrium. Major uterine morphological changes occur in response to cyclical hormonal cues from the ovary and from the embryo during pregnancy. The remodeling of the uterus in response to these stimuli and its return to a basal state may be related to adult stem (or progenitor) cells residing in the individual's endometrial and myometrial compartments (Sozen & Arici, 2006; Blake, 2007). Furthermore, several conditions such as endometrial cancer, endometriosis, and leiomyomas, may be attributed to dysregulations of these same stem cells, or are derived from committed cells that acquire stem-like features (Garget, 2007; Ono *et al*., 2007; Teixeira *et al*., 2008; Garget *et al*., 2008; Hubbard *et al*., 2009; Gargett *et al*., 2012)

The myometrium undergoes significant changes in size and cell properties with the occurrence of specific physiological and pathological conditions such as leiomyomas (Blake, 2007). Each leiomyoma is thought to be a benign monoclonal tumor arising from a single transformed myometrial smooth muscle cell; however, it is not known what leiomyoma cell type is responsible for tumor growth (Sozen & Arici, 2006; Blake, 2007; Ono *et al*., 2012). Recurrent genetic aberrations (trisomy of chromosome 12, deletions in 7q, and mutations affecting the mediator complex subunit 12 (MED12) or the high mobility group AT-hook 2 (HMGA2) have also been described in these uterine tumors. Such abnormalities as well as tumor stem cells are considered to play pivotal roles in the development and growth of leiomyomas (Blake *et al*., 2007; El-Gharib & Elsobky 2010; Bulun, 2013)

Complete characterization of uterine stem/progenitor cells will improve our understanding of the mechanisms supporting physiological regeneration of the female reproductive tract (Garget, 2004). Recent published studies on stem cells and their paracrine interactions with more specialized cell populations within leiomyomas may help establish the missing link between the development of treatments to stop leiomyoma growth and therapies designed to eliminate them (Mas *et al*., 2014; Simon, 2014). In addition, such studies will enhance our understanding of uterine physiology and disease, though advances in the field have been rather slow (Simon, 2014). Thus, this review aimed to address the current paradigm regarding the evidence available on the role of stem/progenitor cells (SC) in the pathogenesis of uterine leiomyomas.

A review of the available literature was conducted using PubMed from 1966 through July 2015 using the following keywords: "leiomyoma", "fibroid", "myoma", "uterine stem cells", "myoma stem cells".

### Adult/Somatic stem cells

Adult stem cells (also called somatic stem cells or tissue-specific stem cells) are rare, undifferentiated cells encountered in adult tissues and organs after embryonic development. These are a subset of cells residing in normal adult tissues that, through asymmetric division, retain their ability to self-renew while producing daughter cells that go on to differentiate and play a vital role in tissue regeneration and repair. Since they are very rare, they are extremely difficult to identify in tissues and lack distinguishing morphological features. As specific adult stem cell markers have not been successfully identified so far, these cells are thus defined by their functional properties: extraordinary self-renewal, high proliferative potential, and ability to differentiate into one or more lineages (Mas *et*

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*al*., 2014; Simon, 2014). In addition, a specific 'niche' is required for each type of adult stem cell to evoke stem cell activity (Eckfeldt *et al*., 2005; Gargett, 2007; Kuçi *et al*., 2009; Maruyama *et al*., 2013).

Other functional properties of adult stem cells include clonogenicity or colony forming unit (CFU) activity, Hoechst 33342 exclusion to identify side population (SP) cells, tissue reconstitution in vivo and DNA synthesis label (bromodeoxyuridine, BrdU) retention for identifying label-retaining cells (LRC). These functional analyses are necessary to single out adult stem cell activity while specific markers for these cells remain unidentified. Ongoing research, however, continues to look for markers of adult stem cells, although few are specific or defining. Adult stem cells play a vital role in tissue homeostasis by supplying replacement cells in routine cellular turnover and repairing injured tissues (Gargett, 2007; Ono *et al*., 2007; Teixeira *et al*., 2008).

Somatic stem cells responsible for the property of quiescence have been used to identify candidate stem cells through their ability to retain the nucleotide analog 5-bromo-2 -deoxyuridine (BrdU) (or 3H-thymidine) for long periods of time, whereas asymmetrically derived lineage-committed daughter cells dilute the BrdU label during rapid proliferation. These so-called label-retaining cells (LRCs) have been shown to correlate with somatic stem cells in various tissues, including the uterine endometrial epithelium and stroma, and have been used as a means of isolating somatic stem cells in tissues where stem cell surface markers have yet to be characterized (Chan & Gargett, 2006; Gargett, 2010).

In the human female reproductive tract, tissue regeneration and growth occurs continuously in each menstrual cycle as well as during pregnancy. The endometrium must regenerate in each menstrual cycle and the uterus must also rapidly grow so as to accommodate the developing fetus. Uterine enlargement during pregnancy can be repeated multiple times throughout a woman's reproductive lifespan. Such cyclic physiologic pattern suggests that myometrial stem/progenitor cells may be present and play a role in myometrial function (Gargett, 2007;Ono *et al*., 2007; Maruyama *et al*., 2010;Maruyama *et al*., 2013).

**Stem cells in myomas**

In recent years, advances in stem cell biology have made it clear that most tissues are extremely plastic and renew through adult stem or progenitor cells. However, only a handful of studies have been performed on the role of adult somatic stem cells in female or male reproductive organs. Unfortunately, studies of adult stem cell biology in the uterus fall far behind other fields of stem cell research even though the uterus undergoes perhaps the most extensive proliferative changes and remodeling in adult mammals in comparison to other organs (Table 1) (Teixeira *et al*., 2008; Maruyama *et al*., 2010; Maruyama *et al*., 2013).

Myomas have been known to have a clonal origin but so far the initiating event remains unknown. Several theories have attempted to explain leiomyoma pathogenesis so far, and recently a role for uterine stem cells has been proposed. One possible explanation for the development of leiomyomas is the dysregulation of mesenchymal stem cell activity. However, there is little data supporting the existence of these cells in benign tumors such as uterine leiomyomas (Chang *et al*., 2010). Reports have demonstrated the existence of myometrial SCs by the identification of label-retaining cells in animal models (Szotek *et al*., 2007) and in the human myometrium (Ono *et al*., 2007) by the side population (SP) method.

The role of a putative stem cell factor (SCF) and its receptor in human myometrial tissue has been analyzed in an attempt to further the understanding of the role(s) of mast cells (MCs) in the uterus (Mori *et al*., 1997). Transcripts for SCF were found in myometrial tissues and myometrial smooth muscle cells. Additionally, enzyme-linked immunosorbent assays demonstrated that cultured myometrial cells produced SCF. Immunohistochemistry staining also revealed the existence of SCF receptors on the surface of myometrial MCs, thus indicating that MC proliferation and differentiation in the myometrium is regulated by SCF secretion from the uterine smooth muscle cells.

Ono *et al.* (2007) described a subset of myometrial cells isolated from non-pregnant human tissue characterized as side-population of myometrial cells (myoSP) by a distinct Hoechst dye efflux pattern. These myoSP cells lay in quiescence and lacked or expressed low levels of myometrial cell markers; however, they but could proliferate and ultimately differentiate into mature myometrial cells in vitro only under hypoxia. Despite the fact that the main population of myometrial cells (myoMP) displayed mature myometrial phenotypes before and after in vitro cultivation, only myoSP was able to generate functional human myometrial tissues efficiently when transplanted into the uteri of extremely immunodeficient mice. MyoSP cells were multipotent and could differentiate into osteocytes and adipocytes in vitro once the appropriate differentiation-inducing conditions were provided. Hence, myoSP displayed phenotypic and functional characteristics of myometrial stem cells. More studies on the area will enhance the understanding of myometrial physiology and the pathogenesis of myometrium-based diseases such as leiomyoma.

Chang *et al.* (2010) studied the differences between leiomyomas and normal myometrium tissue with regards to innate growth capacity by evaluating colony forming ability and mesenchymal stem cell markers based on CD90 expression and side-population (SP) cells as well as differentiation status by CD90 expression patterns after in vitro culture. Leiomyoma cells formed fewer mesenchymal stem cell colonies and displayed less Hoechst dye-excluding side-population (SP) cell activity versus cells isolated from normal myometrium tissue. Leiomyomas appeared more terminally differentiated whereas normal myometrium cells showed heterogeneous expression of CD90, a cell surface marker associated with the differentiation ability of uterine fibroblasts. Such findings suggest that the normal myometrium contains cells with stem/progenitor cell activity not seen in leiomyomas.

Galvez *et al.* (2010) used a simple non-invasive technique to identify a new cell type from mouse adult uterine biopsies (murine adult myometrial precursors or mAMPs). These cells were characterized by surface markers and were positive for CD31, CD34, CD44, CD117, Stro-1 and Sca-1. An analogous cell population (hAMPs) was also obtained in human biopsies. These cells showed ability to differentiate in vitro into a variety of mesodermal (smooth and skeletal muscle, osteoblasts and adipocytes) and epidermal lineages. Once injected into animal models with muscular disease, AMPs could produce new muscle fibers, and boost functional muscular recovery. In addition, these cells stimulated the regeneration of the uterine lining after wound healing, reconstructing the uterine muscular architecture. New vessels both in vitro and in vivo were also formed.

Zhou *et al*. (2011) proposed that human uterine myometrial stem cells exhibit specific phenotypic and functional attributes. Hypoxia appears to aberrantly activate estrogen-signaling pathways in certain myometrial stem cells, leading them to differentiate into leiomyoma cells. This process also shields the cells from physiological apoptosis or dedifferentiation. The authors concluded that hypoxia might be a key element in the pathogenesis of leiomyoma caused by aberrant

Table 1 – Studies on the role of stem cells in leiomyoma pathology

| Author | Objective | Main results | Model |
|---|---|---|---|
| Mas *et al*., 2015 | Test the hypothesis that leiomyoma development may be due to overexpression of HMGA2 in myometrial stem cells using in vitro and in vivo approaches | Overexpression of truncated/short HMGA2 form in myometrial cells result in abnormal proliferation of the SSC niche leading to the formation of leiomyoma-like tissue. | Human and mice |
| Ono *et al*., 2014 | Identify cell surface markers to isolate leiomyoma stem/progenitor cells. | Significantly elevated CD49b and CD34 gene expression in side population cells vs. main population cells | Human |
| Ono *et al*., 2013 | Demonstrate the critical paracrine role of the wingless-type (WNT)/β-catenin pathway in estrogen/progesterone-dependent tumorigenesis, involving LMSP and differentiated myometrial or leiomyoma cells. | Wingless-type (WNT) acts as a paracrine signal from estrogen/progesterone receptor-rich mature cells activating the canonical β-catenin pathway in leiomyoma stem cells, suggesting a paracrine role for the canonical WNT pathway in the growth of leiomyomas. | Human |
| Mas *et al*., 2012 | Obtain human leiomyoma SP cells as candidate tumor-initiating cells and establishment of two leiomyoma SP lines | SP cells from human leiomyomas were isolated, identified, and characterized. Two leiomyoma SP cell lines with a normal karyotype were established | Human and mice |
| Ono *et al*., 2012 | Test the hypothesis that a distinct stem/reservoir cell-enriched population, designated as the leiomyoma-derived side population (LMSP), is responsible for cell proliferation and tumor growth | LMSP, which show stem/reservoir cell characteristics, are necessary for in vivo growth of leiomyoma xenograft tumors. Decreased estrogen and progesterone receptor levels in LMSP suggest an indirect paracrine effect of steroid hormones on stem cells via the mature neighboring cells. | Human and mice |
| Chang *et al*., 2010 | Compare stem/progenitor cell characteristics in both normal myometrium and the corresponding leiomyoma of patients undergoing hysterectomies | Leiomyoma cells form fewer mesenchymal stem cell colonies and exhibit less Hoechst dye-excluding side population (SP) activity, a function associated with progenitor cells in other tissues, than cells isolated from normal myometrium | Human |
| Ono *et al*., 2007 | Describe a subset of myometrial cells isolated from the myometrium of non-pregnant subjects that represents the myometrial stem cell population | When compared to the main population of myometrial cells (myoMP), myoSP remained quiescent, underexpressed or lacked myometrial cell markers; they could also proliferate and eventually differentiate into mature myometrial cells in vitro only under low oxygen concentration. myoSP produced functional human myometrial tissues efficiently when transplanted into the uteri of severely immunodeficient mice. myoSP were multipotent and could differentiate into osteocytes and adipocytes in vitro under appropriate differentiation-inducing conditions | Human and mice |

SP: side-population cells; LMSP: leiomyoma-derived side population; myoSP: side population of myometrial cells

estrogen pathway activation of myometrial stem cells.

Mas *et al*. (2012) tried to isolate and characterize the SP from human leiomyomas, analyzing its clonogenic activity under hypoxic conditions. Since no specific leiomyoma SC markers are available so far, the SP phenotype was used as a general approach to identify candidate leiomyoma SCs. Using these selection criteria, high proliferative clone formation and SP phenotype, the authors identified two human leiomyoma cell lines named LeioSP1 and LeioSP2. Microarray analysis detected 100 upregulated and 53 downregulated genes in leiomyoma SP compared to leiomyoma fragments. Leiomyoma SP cells also lacked typical muscle markers and hormone receptors indicating that they were not yet committed to a specific lineage. These cells showed in vitro and in vivo the ability to differentiate into mesenchymal lineage cell types and to form tissue-like leiomyoma in animal models. These results point to a possible role of stem cells as tumor initiating factors in the development of leiomyomas.

Ono *et al*. (2012) tested the hypothesis that a distinct stem/reservoir cell-enriched population, called the leiomyoma-derived side population (LMSP), could activate cell proliferation and tumor growth. Their results showed that leiomyomas have a lower percentage of SP cells when compared to normal myometrium tissue and that LMSP represent an immature or undifferentiated cell population. LMSP xenografts showed significantly increased proliferative activity in comparison to leiomyoma-derived main population (LMMP) xenografts. LMSP still requires a more thorough characterization so that the multiple mechanisms underlying the pathogenesis of leiomyoma are uncovered.

Recent in vitro data suggests that High Mobility Group A (HMGA), genes which encode DNA-binding nonhistone proteins that control cell growth by indirect regulation of the DNA transcription process, may be involved in the abnormal proliferation pattern seen in myomas. HMGA2 has been implicated in important functions related to cell growth and differentiation in the embryo development process. Disrupted expression in adult tissues plays a vital role in the growth of a variety of mesenchym-al tumors as a result of its oncogenic ability. Apparently, the overexpression of the truncated/short HMGA2 form in myometrial cells might result in abnormal proliferation of the SSC niche leading to the formation of leiomyoma-like tissue (Mas *et al*., 2015).

## CONCLUSION

Myoma development and progression depends on a number of variables: steroid hormones, growth factors, cytokines, chemokines, and extracellular matrix components. Such effect, however, depends on the triggering of an initial tumor-initiating event. Current evidence supports the role of putative stem/progenitor cells found in the human uterus as contributors to the onset of uterine disease such as uterine myomas.

To date, only a handful of studies involving humans have been published describing the presence of somatic stem cells (SSCs) in the myometrium and leiomyomas. However, none has conclusively established the role of such cells in the development of myomas. Although these studies strongly point to the existence of human leiomyoma SP cells possibly playing a role in the development of myomas, huge gaps remain in the literature (Simon, 2014). Studies to identify putative myometrial and leiomyoma specific markers might shed light on the mechanisms involved in the development of myomas and perhaps help develop new nonsurgical noninvasive approaches to treat patients with these tumors. Unfortunately, translating laboratory studies into clinical practice is still far from becoming a reality, as most studies performed with animal models have produced preliminary results at best.

## CONFLICT OF INTERESTS

No conflict of interest have been declared.

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