SciForschen
Open HUB for Scientific Research

ISSN 2472-6990

Cell, Stem cells and Regenerative Medicine

Editorial Volume: 2.1 Open Access

Converting of Myometrial Stem Cells to Tumor-Initiating Cells: Mechanism of Uterine Fibroid Development

Qiwei Yang*, Michael P Diamond and Ayman Al-Hendy

Division of Translation Research, Department of Obstetrics and Gynecology, Augusta University, Medical College of Georgia, Augusta, GA, USA

***Corresponding authors:** Qiwei Yang, Division of Translation Research, Department of Obstetrics and Gynecology, Augusta University, Medical College of Georgia, Augusta, GA, USA, **E-mail:** QYANG@augusta.edu

Received date: 25 Apr 2016; **Accepted date:** 26 Apr 2016; **Published date:** 30 Apr 2016.

Citation: Yang Q, Diamond MP, Al-Hendy A (2016) Converting of Myometrial Stem Cells to Tumor-Initiating Cells: Mechanism of Uterine Fibroid Development. Cell Stem Cells Regen Med 2(1): doi http://dx.doi.org/10.16966/2472-6990.e103

Stem-cell niche is composed of a group of cells within the specific anatomic location that function to maintain stem cells. The niche referring to a microenvironment is capable of generating extrinsic factors that modulate stem cell proliferation and fate determination [1]. During development, various niche factors act on stem cells to alter gene expression, and induce their proliferation or differentiation for the development of the fetus. The highly plastic state of the stem/progenitor cells during developmental and tissue maintenance permits the required flexibility for proper tissue formation and repair. Unfortunately, this plasticity also provides an opportunity for aberrant cellular reprogramming via epigenetic mechanisms due to inappropriate exposures to toxins [2]. The developmental adverse exposure can lead to persistent, life-long effects and resulting in a variety of diseases [3].

Uterine Fibroids (UFs) are monoclonal tumors arising from the myometrium. An increasing body of evidence supports the hypothesis that UFs originate from stem cells in the myometrium, although the specific cell of origin for these tumors has remained elusive [4,5]. The existence of stem cells from myometrium and UFs have been identified, and several studies have been performed to identify tumor-initiating cells in UFs [6-9]. Notably, the difference between myometrial stem cells (MSCs) and fibroid stem cells at DNA level is that *MED12* mutations were found only in fibroid stem cells, but not MSCs [9]. The *MED12* mutations occur in human UF tissues with high frequency in contrast to the findings that other gene mutation and genetic abnormalities occur at relatively low levels in UFs [10,11]. Recent study demonstrated that *MED12* mutation is a driver for promoting development of UFs and genomic instability [12]. Distinct *MED12* mutations have been detected in different fibroid lesions in the same uterus [13] suggesting that the emergence of each *MED12* mutation is an independent event in altered MSCs.

Endocrine disruptors (EDs) are naturally occurring or man-made compounds that may interfere with the endocrine system and cause unfavorable developmental and reproductive effects on human. Increasing studies show that endocrine disruptors may pose the serious risk of many diseases during development [14,15]. A number of studies demonstrate that estrogen clearly influences the proliferation and differentiation of various stem cell types. Epidemiological and experimental studies show that EDs increase the risk of tumorigenesis, especially in the organs that are extremely sensitive to endocrine regulation. In the Eker rat fibroid model, developmental exposures to EDs such as diethylstilbestrol and genistein during a crucial period of uteri development increase the penetrance and growth of UFs concomitantly reprogramming estrogen-responsive gene expression [16-18].

The adverse effect of early life exposure may cause the deregulation of multiple developmental processes including disruption of stem cell niche, developmental reprogramming and altered stem cell characteristics. The somatic stem/progenitor cells from varied tissues and organs have been shown to remain susceptible to EDs [19]. One of the important studies by Bulun's group showed that the differentiated myometrial cells in response to estrogen and progesterone treatment resulted in secretion of wingless-type (WNT) ligands, which induced nuclear translocation of β-catenin in stem/progenitor cells from UFs. The activation of β-catenin pathway ultimately enhanced the cell growth and proliferation of these stem/progenitor cells [20].

Taken together, emerging studies suggest that the developmental exposure to EDs and other toxins may result in genetic/epigenetic alterations and aberrant niche of MSCs, thereby converting the MSCs to tumor-initiating cells via a variety of signaling pathways. Thus further understanding of contributions of the stem cell micro-environment/reprogramming to development of UFs will be important for future clinical progress.

Acknowledgement

This work was supported in part by an Augusta University Startup package, the National Institutes of Health grant HD04622811 (to AA), and the Augusta University Intramural Grants Program (QY).

Conflict of Interest

None of the authors have a financial relationship with a commercial entity with an expressed interest in the subject-matter of this manuscript.

References

1. Li L, Neaves WB (2006) Normal stem cells and cancer stem cells: the niche matters. Cancer Res 66: 4553-4557.
2. Walker CL, Ho SM (2012) Developmental reprogramming of cancer susceptibility. Nat Rev Cancer 12: 479-486.
3. Prins GS, Calderon-Gierszal EL, Hu WY (2015) Stem Cells as Hormone Targets That Lead to Increased Cancer Susceptibility. Endocrinology 156: 3451-3457.
4. Linder D, Gartler SM (1965) Glucose-6-phosphate dehydrogenase mosaicism: utilization as a cell marker in the study of leiomyomas. Science 150: 67-69.
5. Bulun SE (2013) Uterine fibroids. N Engl J Med 369: 1344-1355.

6. Ono M, Maruyama T, Masuda H, Kajitani T, Nagashima T, et al. (2007) Side population in human uterine myometrium displays phenotypic and functional characteristics of myometrial stem cells. Proc Natl Acad Sci U S A 104: 18700-18705.

7. Chang HL, Senaratne TN, Zhang L, Szotek PP, Stewart E, et al. (2010) Uterine leiomyomas exhibit fewer stem/progenitor cell characteristics when compared with corresponding normal myometrium. Reprod Sci 17: 158-167.

8. Mas A, Cervello I, Gil-Sanchis C, Faus A, Ferro J, at al. (2012) Identification and characterization of the human leiomyoma side population as putative tumor-initiating cells. Fertil Steril 98: 741-751 e746.

9. Ono M, Qiang W, Serna VA, Yin P, Coon J St, et al. (2012) Role of stem cells in human uterine leiomyoma growth. PLoS one 7: e36935.

10. Yang Q, Mas A, Diamond MP, Al-Hendy A (2015) The Mechanism and Function of Epigenetics in Uterine Leiomyoma Development. Reprod Sci 23: 163-175.

11. Yang Q, Diamond MP, Al-Hendy A (2016) Early Life Adverse Environmental Exposures Increase the Risk of Uterine Fibroid Development: Role of Epigenetic Regulation. Front pharmacol 7: 40.

12. Mittal P, Shin YH, Yatsenko SA, Castro CA, Surti U, et al. (2015) Med12 gain-of-function mutation causes leiomyomas and genomic instability. J Clin Invest 125: 3280-3284.

13. Makinen N, Mehine M, Tolvanen J, Kaasinen E, Li Y, et al. (2011) MED12, the mediator complex subunit 12 gene, is mutated at high frequency in uterine leiomyomas. Science 334: 252-255.

14. Heindel JJ, Balbus J, Birnbaum L, Brune-Drisse MN, Grandjean P, et al. (2015) Developmental Origins of Health and Disease: Integrating Environmental Influences. Endocrinology 156: 3416-3421.

15. Wong RL, Wang Q, Trevino LS, Bosland MC, Chen J, et al. (2015) Identification of secretaglobin Scgb2a1 as a target for developmental reprogramming by BPA in the rat prostate. Epigenetics 10: 127-134.

16. Cook JD, Davis BJ, Cai SL, Barrett JC, Conti CJ, et al. (2005) Interaction between genetic susceptibility and early-life environmental exposure determines tumor-suppressor-gene penetrance. Proc Natl Acad Sci U S A 102: 8644-8649.

17. Cook JD, Davis BJ, Goewey JA, Berry TD, Walker CL (2007) Identification of a sensitive period for developmental programming that increases risk for uterine leiomyoma in Eker rats. Reprod Sci 14: 121-136.

18. Greathouse KL, Bredfeldt T, Everitt JI, Lin K, Berry T, et al. (2012) Environmental estrogens differentially engage the histone methyltransferase EZH2 to increase risk of uterine tumorigenesis. Mol Cancer Res 10: 546-557.

19. Kopras E, Potluri V, Bermudez ML, Williams K, Belcher S, et al. (2014) Actions of endocrine-disrupting chemicals on stem/progenitor cells during development and disease. Endocr Relat Cancer 21: T1-12.

20. Ono M, Yin P, Navarro A, Moravek MB, Coon J St, et al. (2013) Paracrine activation of WNT/beta-catenin pathway in uterine leiomyoma stem cells promotes tumor growth. Proc Natl Acad Sci U S A 110: 17053-17058.