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Proceedings from the NICHD Conference on the Uterine Fibroid Research Update Workshop

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Abstract

The purpose of the National Institutes of Health conference Fibroid Research Workshop in September 2007 was to bring Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) funded fibroid investigators together to discuss basic science and clinical research advances on uterine leiomyomata. General topics included advances in epidemiology, etiology, therapeutic approaches, and clinical trial challenges; suggestions for advancement basic understanding, clinical intervention, clinical trials, and future directions were highlighted.

Keywords

Leiomyoma; myometrium; epidemiology; etiology; therapy; clinical trials

Introduction

The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development sponsored a Uterine Fibroid Research Update Workshop. The focus of this initiative was to review the latest research findings among NIH-supported researchers in uterine leiomyomata. Investigators reviewed data on leiomyoma epidemiology, etiology, therapy,

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and clinical trial challenges. The findings of this conference are summarized in this document, with resulting manuscripts included.

Epidemiology

Racial Disparity and Assisted Reproductive Technologies

In a retrospective study evaluating outcomes of IVF in women with leiomyomata, race was self-identified but independently verified. African American women had higher utilization rates for ART, and their outcomes were worse than those of other races. The spontaneous abortion rate was significantly higher among African American women. Presence of leiomyomata was associated with a reduced likelihood of pregnancy, irrespective of race. African American women had significantly greater numbers of leiomyomata. When comparing racial groups and controlling for the presence of fibroids, no differences in pregnancy outcomes were observed (1).

Racial Disparity and Genetics

Several studies have demonstrated an increased prevalence of leiomyomata in African-American women compared to Caucasian women. African-American women were diagnosed earlier (31yo vs. 37yo.), and were more likely to have severe symptoms (30% vs. 15%). In support of a heritable predisposition to development of leiomyoma, genetic syndromes such as hereditary leiomyomatosis and renal cell cancer demonstrate alterations in specific genes, such as fumarate hydratase. Other identified candidate genes include *HMGA2*, *HMGA1*, *CYP11A1*, *CYP11B1*, and *MORF*. Expression of *HMGA2* exhibited greater variation in African American women compared with Caucasian women. Using single nucleotide polymorphism (SNP) analysis, there was a significant linkage of the C allele of a 3' untranslated region of *HMGA2* in Caucasian women (2).

Racial Disparity and Catechol-O-methyltransferase polymorphisms

Catechol-O-methyltransferase (*COMT*) converts catechol estrogens into methoxy derivatives that have hormonal and metabolic effects. *COMT* is overexpressed in leiomyoma compared to adjacent myometrium. The wild-type *COMT* val/val variant has significant enzymatic activity. The *COMT* val/met polymorphism has intermediate activity, whereas the met/met variant has very low enzymatic activity due to thermal instability. The high-activity *COMT* val/val polymorphism is associated with increased risk of leiomyoma. The *COMT* val/val genotype is more prevalent in African American women and might be an explanatory factor for their higher risk of uterine leiomyomata. *COMT* inhibitors might be a potential medical intervention for leiomyomata (3).

Leiomyomata and Miscarriage

A prospective study was performed to investigate the association of leiomyomata with spontaneous abortion for a cohort in which fibroids of 0.5 cm or more were documented early in pregnancy. An ultrasound was scheduled as close to 5–6 weeks' gestation as possible, with further data obtained at 10–12 weeks and 22–24 weeks to ensure that all pregnancy losses are reported. The presence of fibroids is not independently associated with risk of miscarriage. With the exception of submucous fibroids, there was no evidence that

fibroid characteristics increased the risk of miscarriage. However, additional evaluation is required before reaching conclusions about possible effects of smaller, intramural, mucous fibroids on pregnancy (4).

Psychosocial Stress and Leiomyomata

Psychological stress has been associated with mental and physical health outcomes such as obesity, atherosclerosis, and hypertension—all potential risk factors for leiomyoma development. Stress could increase risk of uterine fibroids through several possible mechanisms, including disruption of the HPA axis. Data suggested that a link might exist between stress and the number of leiomyoma. Additional analyses using multivariate models are planned. In addition, plans to examine perceived racism as a chronic stressor and as a risk factor for fibroids in African American women are under development. Sensitivity analyses and Bayesian analyses will be conducted to evaluate reverse causation.

Etiology

Altered Cell Differentiation

Leiomyoma surgical specimens demonstrated reduced expression of gene products involved in retinoic acid (RA) production and increased expression of gene products involved in RA degradation. Furthermore, leiomyoma tissues exhibited more rapid metabolism of RA when the hormone was added exogenously. When RA was added to immortalized leiomyoma cells in tissue culture, expression of genes involved in RA production increased to expression levels found in myometrial cells; conversely, genes involved in RA degradation decreased to expression levels found in myometrial cells. Retinoic acid treatment of immortalized leiomyoma cells altered expression of many genes encoding extracellular matrix (ECM) proteins, and levels of expression resembled expression levels observed in myometrial cells. In contrast, treatment of immortalized myometrial cells with TGF- β 3 caused immortalized myometrial cells to develop a leiomyoma-like ECM phenotype (5–10).

Smooth Muscle Hyperproliferation

CCN5 is a secreted matricellular protein that is down-regulated in human leiomyomata. It is unique among the CCN family of proteins because it does not increase proliferation, motility, or expression of matrix metalloproteinases (MMPs). CCN5 function seems to vary by cell type; in some cells, CCN5 is a scaffolding protein. *CCN5* knockdown increases uterine smooth muscle cell (SMC) motility by altering the α -actin cytoskeleton. Furthermore, *CCN5* expression was rapidly decreased when SMCs received a signal to proliferate. Collagen types I and II were significantly down-regulated in uterine SMCs when exposed to CCN5 protein. *CCN5* is an important regulator of SMC function in both normal and diseased states (11).

Progesterone Action

Progestins and antiprogestins have important biologic and therapeutic effects on uterine leiomyoma. Mechanistically, progesterone receptor (PR) - ligand complexes interact with promoters of a number of genes and regulate gene expression in leiomyoma cells. The products of these genes reduce apoptosis and enhance proliferation (e.g. *BCL2*, *KLF11*),

thereby promoting growth of leiomyomata. Conversely, progesterone antagonists exert therapeutic effects via targeting of these genes and reversal of the mitogenic effects of progesterone. Furthermore, PR binds at sites throughout the entire genome at previously unrecognized sites. In addition, effects of progestins on leiomyoma growth potentially include non-classical signaling through interaction with membrane progestin receptors (12–15).

Aromatase Regulation by Leptin

Leptin is a plausible regulator of aromatase, given the coexpression of leptin and aromatase by adipocytes. Leptin also stimulates collagen production and may therefore play a role in leiomyoma formation. Treatment of primary leiomyoma cells in culture with leptin resulted in increased aromatase expression. Furthermore, leptin treatment resulted in phosphorylation of JAK-2 and STAT3, while cotreatment with a JAK-2 phosphorylation inhibitor prevented the leptin-regulated increase in aromatase expression. Chromatin immunoprecipitation (ChIP) analysis demonstrated STAT-3 binding to the aromatase promoter I.4, suggesting a possible mechanism for leptin regulation of aromatase in leiomyomata.

Altered Mechanical Homeostasis

Clinically, leiomyomata are firm tumors. Cells within a leiomyoma grow and proliferate in a milieu of increased mechanical stress. Additionally, the ECM secreted by leiomyoma cells was disordered and featured altered expression of proteins, such as versican. The increased mechanical stress was accompanied by activation of the small GTP-binding protein Rho, and increased levels of Rho-GEF, AKAP13. Studies have shown that the apoptotic index is reduced in leiomyomata, and activation of Rho has been shown to promote a proliferative phenotype in some cells. Application of mechanical strain to myometrial or leiomyoma cells in culture revealed fundamental differences in levels of Rho activation. Leiomyoma cells may secrete more ECM as a result of the increased mechanical stress, but they do so in a disordered and dysregulated fashion. Whether application of mechanical stress would alter the growth of leiomyoma cells remains to be tested (16).

Extracellular Matrix Regulation

Halofuginone inhibited TGF- β signaling by leiomyoma SMCs. Furthermore, proliferation assays revealed a dose-dependent inhibition of DNA synthesis by halofuginone for both leiomyoma and myometrial cells. Halofuginone reduced mRNA levels of collagen types I and III in leiomyoma and myometrial SMCs. Furthermore, halofuginone-mediated inhibition of myometrial and leiomyoma cell proliferation was reversible when the drug was removed. Adding monomeric bovine collagen type I reduced the inhibitory effect of halofuginone on leiomyoma cell proliferation. It was the inhibition of collagen production that appeared to be responsible for proliferation inhibition. Monomeric collagen stimulated growth of leiomyoma cells (17).

Fibrosis Regulation

In many ways, fibroid development resembles the process of wound healing. Among the factors that are shared between leiomyoma and wound healing are: vascular growth, blood

coagulation, prolonged inflammation, tissue formation, contraction (only in scar formation), and cell transformation into fibroblastic phenotype. Leiomyomata from African-American women expressed higher levels of CTGF than those from their Caucasian women. The pro-fibrotic action of TGF- β involved CTGF induction, and mediated its action, in part, through TGF- β , a principal mediator of tissue fibrosis. The TGF- β receptor signaled through MAPK. Furthermore, CCN-2, -3, and -4 were down-regulated at the tumor level. The cellular-level effects of CTGF in leiomyoma are not fully understood (18–20).

Cell Signaling Defects

Two well studied cell signaling pathways that drive leiomyoma growth are TGF- β and p27/Cdk2. The TGF- β signaling components were overexpressed in human leiomyoma, and both primary tumors and a leiomyoma cell lines expressed TGF- β receptors type I and II. Treatment of female Eker rats with a TGF- β receptor inhibitor reduced the incidence of leiomyoma. Functional inactivation of p27 in leiomyoma occurred via two mechanisms: loss of expression and cytoplasmic sequestration. The loss of p27 function and consequent elevation of Cdk2 activity might regulate estrogen receptor function and affect Rho signaling by inhibiting the interaction of estrogen receptor and Rho (21).

Leiomyoma Variation in One Patient

To eliminate the heterogeneity between leiomyoma from different patients, microarrays were conducted on different leiomyoma within a single woman. There was some heterogeneity in gene expression among leiomyomata compared with patient-matched myometrium, there was decreased expression of fibulin 3 (85% of pairs from 5 patients), Mst4 (38%), and MMP-7 (77%), while desmoglein 2 (54%), MMP-11 (92%), and PKC- β 1 (23%) expression was generally increased in leiomyomas when confirmed by real time RT-PCR or western blot. Overall, genes involved in proliferation were increased, while genes involved in growth inhibition and apoptosis were decreased in leiomyomas from the same patient. Furthermore, genes involved in invasion, migration, and metastasis were decreased in leiomyomata (22).

Therapeutic Approaches

Antiprogesterin (Mifepristone)

Mifepristone at 5mg daily resulted in an improvement in quality of life by 135% using the UFS-QOL, while pain, bleeding, and uterine size decreased by 60%, 80%, and 47% respectively. There was no evidence of endometrial hyperplasia or cellular atypia by endometrial biopsy, although proliferative cystic glandular dilation with densely packed stroma was noted. Lower doses of 2.5mg per day for a 6 months resulted in an improvement in quality of life of up to 110%. Furthermore, half of the patients became amenorrheic, and uterine volume decreased by 18%. Despite this modest decrease in uterine and leiomyoma size, there was notable improvement in pain and bleeding (23).

Antiprogesterin (CDB-2914)

CDB-2914, an investigational anti-progesterin, was used to treat women with documented leiomyoma in a randomized, placebo-controlled study. Over the 3 month study period, the

largest leiomyoma of placebo-treated patients increased in size by 16%, while women treated with CDB-2914 had a decrease in leiomyoma size of 32% for the 10mg dose, and 15% for 20mg dose. Reduction in leiomyoma size was found for those tumors 2cm or larger in diameter. Treatment with CDB-2914 also induced amenorrhea. One patient in the treated arm was diagnosed with endometrial hyperplasia without atypia. Surgical specimens obtained are currently undergoing microarray analysis evaluation (24).

Resveratrol

Resveratrol, a dietary phytoalexin, has known anti-tumor effects. Resveratrol induces apoptosis in human uterine leiomyoma cells *in vitro*. In addition, resveratrol inhibited cellular proliferation and arrested the cell cycle of the leiomyoma cells in the G1 phase and inhibited the cell-cycle progression from the G1 to S phase. The apoptotic effects of resveratrol were associated with reduced expression of anti-apoptotic proteins Bcl-2, Bcl-xL, and Mcl-1 and induction of the pro-apoptotic proteins Bak and Bad in human leiomyoma cells. Resveratrol treatment reduced mRNA and protein expression of collagen types I and III in a dose-dependent manner in human uterine leiomyoma cells.

Gene Therapy

Leiomyoma cell proliferation in the Eker rat model was inhibited by a thymidine kinase-gancyclovir (TK/GCV) expressing adenovirus. Analysis of the tumors after direct injection of adenovirus suggested that TK/GCV virus induced apoptosis in the Eker rat leiomyoma cells, as suggested by decreased Bcl-2, cyclin D1, PCNA, and PARP1. Furthermore, proliferation was inhibited. In fact, virus was detected only in tumor by PCR evaluation, and at low levels in liver in about 30% of animals studied. Using a thymidine kinase-gancyclovir (TK/GCV) expressing adenovirus, that the number of cells that were killed was greater than expected based upon the number of cells transfected, suggesting that there was a 'bystander effect' (25,26).

Clinical Trial Challenges

Factors Influencing Recruiting for Clinical Trials (Site 1)

There was very limited success in recruiting subjects with television spots, newspaper advertisements, recruitment at colleges, churches, or public housing settings. Unfortunately, IRB issues prevented an internet web site from becoming a recruiting tool. After a year of slow accrual, the investigators enlisted the support of recruitment liaisons to drive the research into the community. Overall, there is a need to tailor recruitment methods to the population. A lack of community awareness of clinical trials seemed to be a bigger barrier than the cultural differences between the investigators and the community.

Factors Influencing Recruiting for Clinical Trials (Site 2)

On average, randomized clinical trials enrolled 36.6% of screened subjects and 28% of subjects completed the studies. In general, the greatest drop-out occurred between screening and enrollment. Highest completion rates were in studies involving surgical treatment of all subjects, while having strict inclusion criteria and uncertain treatment assignments appeared to negatively affect accrual. The most effective means for recruitment were television, radio,

and newspaper advertisements that were likely to reach target groups; the Internet; word of mouth; and community outreach. Providing a variety of study options maximized fibroid study enrollment. Developing partnerships and collaborations in the community were critical (27).

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Future Research Directions

- Disseminate knowledge to educate clinicians.
- Further define genetic studies associated with the risk of fibroids.
- Identify opportunities for professional partnerships among scientific investigators and physicians.
- Initiate a pathway map that highlights where knowledge intersections and knowledge gaps lie.
- Utilize tissue samples to the extent possible for single nucleotide polymorphism (SNP) analysis, proteomics, cell culture, and investigations involving SERMS or SPRMS.
- Collaborate in expanding current tissue banking systems.
- Expand the use of minimally invasive tools, such as RF devices and ultrasound that have potential for early detection and treatment interventions.
- Assess polydrug (multiple drug) therapy to target different parts of the pathway.
- Develop boilerplate language for consent regarding genetic information
- Develop mechanisms to track ongoing trials so that potential study participants who are ineligible for a particular protocol might be referred to other trials
- Develop prevention strategies for uterine fibroids.
- Develop appropriately designed incidence and prevalence studies of women from all racial and ethnic groups.
- Identify biomarkers to identify subgroups of women that might benefit from targeted therapies.
- Emphasize translational research as a way to develop model systems to validate treatment options.
- Consider the initiation of a fibroid clinical trials network.