Can you share the main goals of your studies into cervical remodelling?

The key objective of our research programme is to gain insight into the molecular mechanisms by which the cervix remodels prematurely. In order to understand premature cervical remodelling we must also understand normal physiological cervical remodelling at term. We hope this knowledge will lead to improved and more effective therapies for the prevention of preterm labour, as well as for developing clinical tools for early and accurate detection of preterm birth risk.

Why has most cervical change research focused on the end of pregnancy?

There are a number of reasons why researchers initially focused on this. For example, uterine contraction and cervical changes at the end of pregnancy are more apparent than the subtle changes that occur early on. Also, reduced function of the pregnancy maintaining hormone, progesterone, does not occur until the latter stages, which led to the thinking that key events begin very late in pregnancy. In addition, for practical and ethical reasons, it is not possible to obtain tissues earlier in pregnancy, and thus much work from human as well as animal studies has been conducted using tissue collected at term or shortly after delivery.

Who do you collaborate with in order to further your cervical change research?

My laboratory focuses on the biology and molecular mechanisms of this process and a key collaboration in this project is with Dr Kristin Myers, Assistant Professor in the Department of Mechanical Engineering at Columbia University, USA. Myers and her group have the expertise to determine the mechanical properties of soft tissues such as the cervix. They are working closely with us to understand, from a mechanical standpoint, the properties of cervical remodelling in infection-mediated premature remodelling as compared to term remodelling.

As a professor at the University of Texas Southwestern (UTSW) Medical Center, what facilities and resources are made available to you?

Our resources in the Department of Obstetrics and Gynecology’s Division of Basic Reproductive Biology Research and the Green Center for Reproductive Biological Sciences are extensive. With five Nobel laureates, 23 members of the National Academy of Sciences and 13 members of the Howard Hughes Medical Institute, UTSW provides an exceptional and highly interactive scientific and intellectual environment.

Our basic research programme benefits from the outstanding clinical expertise within our department and thus helps ensure that the design of our studies in animal models is clinically relevant. The Green Center, which is the research arm of the Obstetrics and Gynecology Department, is comprised of basic researchers that are leaders in the fields of genomics, transcription and non-coding ribonucleic acids (RNAs) and collaborations with these investigators have allowed us to utilise the latest genomic approaches to our research programme. The Department oversees one of the busiest maternity programmes in the country (10,000 births per year) and our clinical obstetrics and gynaecological programme is ranked sixth in the US News & World Report.

How important is it to foster close relationships with other laboratories in your work?

The University has an extensive array of core laboratories that we depend on for our studies. This includes the Live Cell Imaging facility that houses state-of-the-art microscopes which allow second harmonic imaging, transmission electron microscopy and scanning electron microscopy. Collaborations with Dr Kate Luby-Phelps, Director of the Live Cell Imaging and Electron Microscopy Cores, as well as...
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Preterm birth research

Promising preterm birth research

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Do you foresee any new research directions being followed in your laboratory in the near future?

While our focus on cervical remodelling in term and preterm birth will remain the same, we are currently taking several new approaches to tackle this question. These include using high-throughput transcriptome profiling studies to identify coding and non-coding RNAs that regulate term and infection-mediated preterm ripening. Preliminary data suggest that this approach holds great promise in providing new insights.

In addition to our continued efforts to focus on the cervical extracellular matrix (ECM), we will also devote more time to understanding how hyaluronan regulates epithelial barrier function to protect against ascending infection. Another recent finding from our laboratory that proteoglycans play a key role in modulating the ECM architecture is an exciting discovery that will likely lead to new research projects in the near future.

Second harmonic generation (SHG) reveals transition from straight, thin collagen fibres in nonpregnant cervix (left) to curved, thick fibres in late pregnancy (right).
DEFINING GENE EXPRESSION PROGRAMMES IN CERVICAL RIPENING: ROLES FOR NON-CODING RNAs

OBJECTIVES
To identify the molecular mechanisms driving cervical remodelling in term pregnancy and in defined models of preterm birth with the goal of understanding physiology and pathophysiology and its application toward development of preventive therapies or tools for early and accurate detection of preterm birth risk.

KEY COLLABORATORS
Dr. Kate Luby-Phelps, Professor of Cell Biology and Director of Live Cell Imaging and Electron Microscopy Core Facility, The University of Texas Southwestern (UTSW) Medical Center, USA

Dr. W. Lee Kraus, Director, Green Center for Reproductive Sciences and Professor of Obstetrics and Gynecology and Pharmacology, The University of Texas Southwestern (UTSW) Medical Center, USA

Dr. Xingde Li, Professor of Biomedical Engineering, Johns Hopkins University, USA

Dr. Kristin Myers, Assistant Professor in the Department of Mechanical Engineering, Columbia University, USA

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Mala Mahendroo is a professor in the Department of Obstetrics and Gynecology, and a member of the Green Center for Reproductive Biological Sciences and the Integrative Biology Programme at the UTSW Medical Center. She obtained her PhD in Biochemistry and Molecular Biology from UTSW in 1993 and carried out postdoctoral work in the Department of Molecular Genetics. Her research interests revolve around understanding the molecular physiology of cervical remodelling in term and preterm birth. Through collaborative studies her interests lie in connecting biological understanding with tissue mechanics of the cervix and the development of clinical tools for detection of preterm birth risk.

PHYSIOLOGICAL DISTINCTIONS
One of the factors of premature cervical ripening that Mahendroo has recognised is that it is not simply a case of normal processes occurring earlier than they should. Rather, it is a separate process that is taking place defined by completely different factors from term ripening, such as a large influx and activation of proinflammatory cells, lower estradiol levels and the central role played by prostaglandins, as Mahendroo explains further: “Understanding these distinctions is key for the development of targeted therapies for prevention of preterm birth and early and accurate detection of premature cervical ripening”. To illuminate this process further, the team has been identifying the physiological differences between ripening induced by inflammation and infection and progesterone withdrawal at term and preterm.

They used two specific preterm birth mouse models where birth was induced early by either administering a prostaglandin antagonist, which is designed to mimic progestosterone withdrawal, or by administering lipopolysaccharide, which mimics bacterial infection. The results of this work have led the researchers to further explore the role prostaglandins play in preterm ripening initiated by lipopolysaccharide. Based on current studies, the team has concluded that progesterone withdrawal occurs in both term and preterm birth, but they have also come to the conclusion that prostaglandins are only required for premature cervical remodelling induced in a model of bacterial infection. Mahendroo points out that if prostaglandins play a similar role in women then the clinical use of prostaglandins to induce cervical softening prior to labour induction, likely mimics the inflammation-mediated pathway of cervical ripening.

THE CRITICAL ROLE OF HYALURONAN
Some of the UTSW group’s latest work revolves around the way that hyaluronan (HA), a nonsulphated glycosaminoglycan, maintains the cervical epithelial barrier through local synthesis. With the hypothesis that the absence of HA in the cervix would result in defective cervical ripening and labour, the team produced mice that lacked HA synthase genes in the lower reproductive tract. Surprisingly, it was found that the mice lacking HA had normal timing of parturition and normal changes in cervical mechanical strength, so it was deduced that HA is not essential in cervical extracellular matrix reorganisation.

“This finding debunked the long held belief that HA was critical in regulating cervical tissue mechanics,” remarks Mahendroo.

They also learnt that loss of HA results in defects in the functional and mucosal epithelial barrier properties, leading to an increased susceptibility to bacterial infection-mediated preterm birth. Mahendroo details the significance of this work: “These novel findings suggest that therapies to promote cervical epithelial health may provide more effective protection against premature birth rather than disruption of the cervico-vaginal microbiome with prophylactic antibiotic treatment”. The new knowledge that compromised barrier function and reduced HA levels are a risk factor offers exciting potential to develop novel therapies.

LEVERAGING BIOLOGICAL DISCOVERIES
Mahendroo’s investigations have provided new insights into cervical function and processes and significantly added to understanding of cervical biology in relation to preterm birth. For example, the team has deduced that term ripening is not characterised by leukocyte infiltration, activation and subsequent release of proteases, and that specific changes in collagen processing, assembly and structure begin in the very early days of pregnancy and carry on through the term. Mahendroo is particularly pleased about the new understanding they have brought to the mechanisms by which the cervical epithelium play a critical role in protection against premature birth and the finding that HA is critical to maintaining epithelial health.

With the opportunity to take their new knowledge and build on it with collaborators, the UTSW group is optimistic about what they can achieve, as Mahendroo reveals: “These collective findings have led us to work with bioengineers and mechanical engineers in the hope of leveraging our biological discoveries into the development of a clinical tool that identifies premature cervical changes in collagen structure as a harbinger for preterm birth”. Such a tool would offer expectant mothers and health professionals vital information to prepare for preterm birth and minimise its potential damaging consequences.