Journals in Science

Advances in Therapy

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Update on Emergency Contraception

P. M. Fine

Emergency contraception is a woman's last chance to prevent unintended pregnancy. Ulipristal acetate, a selective progesterone receptor modulator, when taken as a single 30 mg dose, is a new, safe, and effective emergency contraceptive that can be used from the first day and up to five days following unprotected intercourse. The older progesterone-only emergency contraceptive, levonorgestrel, is taken as two 0.75 mg pills twelve hours apart (Next Choice; Watson Pharmaceuticals Inc., Morristown, NJ, USA) or a single 1.5 mg pill (Plan B One-Step; Watson Pharmaceuticals Inc.) and is approved for only seventy-two hours after unprotected intercourse. During clinical development, ulipristal acetate has been shown to be more effective than levonorgestrel in delaying or inhibiting ovulation. A recent meta-analysis of two randomized clinical trials showed ulipristal acetate to have a pregnancy risk 42 percent lower than levonorgestrel up to seventy-two hours and 65 percent lower in the first twenty-four hours following unprotected intercourse. Moreover, when taken beyond seventy-two hours, significantly more pregnancies were prevented with ulipristal acetate than with levonorgestrel. Side effects are mild and similar to those seen with levonorgestrel. Ulipristal acetate was approved for emergency contraception by the U.S. Food and Drug Administration in August 2010 and has been launched in the United States as ella (Watson Pharmaceuticals Inc.) since December 1, 2010. ella is prescription only and is priced comparable to Plan B One-Step.

Cell

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Reference Maps of Human ES and iPS Cell Variation Enable High-Throughput Characterization of Pluripotent Cell Lines

C. Bock et al.

The developmental potential of human pluripotent stem cells suggests that they can produce disease-relevant cell types for biomedical research. However, substantial variation has been reported among pluripotent cell lines, which could affect their utility and clinical safety. Such cell-line-specific differences must be better understood before one can confidently use embryonic stem cells or induced pluripotent stem (iPS) cells in translational research. Toward this goal we have established genome-wide reference maps of DNA methylation and gene expression for twenty previously derived human embryonic stem cell lines and twelve human iPS cell lines, and we have measured the in vitro differentiation propensity of these cell lines. This resource enabled us to assess the epigenetic and transcriptional similarity of embryonic stem cells and iPS cells and to predict the differentiation efficiency of individual cell lines. The combination of assays yields a scorecard for quick and comprehensive characterization of pluripotent cell lines.

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Endocrine Regulation of Male Fertility by the Skeleton

F. Oury et al.

Interactions between bone and the reproductive system have until now been thought to be limited to the regulation of bone remodeling

by the gonads. The authors now show that, in males, bone acts as a regulator of fertility. Using coculture assays, they demonstrate that osteoblasts are able to induce testosterone production by the testes, though they fail to influence estrogen production by the ovaries. Analyses of cell-specific loss- and gain-of-function models reveal that the osteoblast-derived hormone osteocalcin performs this endocrine function. By binding to a G protein-coupled receptor expressed in the Leydig cells of the testes, osteocalcin regulates in a CREB-dependent manner the expression of enzymes that is required for testosterone synthesis, promoting germ cell survival. This study expands the physiological repertoire of osteocalcin and provides the first evidence that the skeleton is an endocrine regulator of reproduction.

Cell Stem Cell

Volume 8, Number 1
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A Human iPSC Model of Hutchinson Gilford Progeria Reveals Vascular Smooth Muscle and Mesenchymal Stem Cell Defects

J. Zhang et al.

The segmental premature aging disease Hutchinson-Gilford Progeria syndrome (HGPS) is caused by a truncated and farnesylated form of Lamin A called progerin. HGPS affects mesenchymal lineages, including the skeletal system, dermis, and vascular smooth muscle (VSMC). To understand the underlying molecular pathology of HGPS, the authors derived induced pluripotent stem (iPS) cells from HGPS dermal fibroblasts. The iPS cells were differentiated into neural progenitors, endothelial cells, fibroblasts, VSMCs, and mesenchymal stem cells (MSCs). Progerin levels were highest in MSCs, VSMCs, and fibroblasts, in that order, with these lineages displaying increased DNA damage, nuclear abnormalities, and HGPS-VSMC accumulating numerous calponin-staining inclusion bodies. Both HGPS-MSC and -VSMC viability was compromised by stress and hypoxia in vitro and in vivo (MSC). Because MSCs reside in low oxygen niches in vivo, the authors propose that, in HGPS, this causes additional depletion of the MSC pool responsible for replacing differentiated cells lost to progerin toxicity.

Volume 8, Number 2
February 4, 2011

Policy Uncertainty and the Conduct of Stem Cell Research

A.D. Levine

A survey of U.S. stem cell scientists shows that uncertainty following the legal challenge to the Obama Administration's human embryonic stem cell research policy has negative scientific and economic impacts and affects a range of stem cell scientists, not just those working with human embryonic stem cells. The international implications of these results are also discussed.

Volume 8, Number 3
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Short-Term Immunosuppression Promotes Engraftment of Embryonic and Induced Pluripotent Stem Cells

J.I. Pearl et al.

Embryonic stem cells are an attractive source for tissue regeneration and repair therapies because they can be differentiated into virtually any cell type in the adult body. However, for this approach to succeed, the transplanted embryonic stem cells must survive long enough to generate a therapeutic benefit. A major obstacle facing the engraftment of embryonic stem cells is transplant rejection by the immune system. Here the authors show that blocking leukocyte co-stimulatory molecules permits embryonic stem cell engraftment. The authors demonstrate the success of this immunosuppressive therapy for mouse embryonic stem cells, human embryonic stem cells, mouse induced pluripotent stem (iPS) cells, human iPS cells, and more differentiated embryonic stem cell/(iPS cells) derivatives. Additionally, the authors provide evidence describing the mechanism by which inhibition of co-stimulatory

molecules suppresses T cell activation. This report describes a short-term immunosuppressive approach capable of inducing engraftment of transplanted embryonic stem cells and iPS cells, providing a significant improvement in our mechanistic understanding of the critical role co-stimulatory molecules play in leukocyte activation.

The Adult Mouse and Human Pancreas Contain Rare Multipotent Stem Cells that Express Insulin

S. R. Smukler et al.

The search for putative precursor cells within the pancreas has been the focus of extensive research. Previously, the authors identified rare pancreas-derived multipotent precursor (PMP) cells in the mouse with the intriguing capacity to generate progeny in the pancreatic and neural lineages. Here, the authors establish the embryonic pancreas as the developmental source of PMPs through lineage-labeling experiments. They also show that PMPs express insulin and can contribute to multiple pancreatic and neural cell types in vivo. In addition, the authors have isolated PMPs from adult human islet tissue that are also capable of extensive proliferation, self-renewal, and generation of multiple differentiated pancreatic and neural cell types. Finally, both mouse and human PMP-derived cells ameliorated diabetes in transplanted mice. These findings demonstrate that the adult mammalian pancreas contains a population of insulin(+) multipotent stem cells and suggest that these cells may provide a promising line of investigation toward potential therapeutic benefit.

Contraception

Volume 82, Number 6
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Hormonal Evaluation and Midcycle Detection of Intrauterine Glycodelin in Women Treated with Levonorgestrel as in Emergency Contraception

M. Durand et al.

Background: The study was conducted to assess the effects of levonorgestrel (LNG) on hormonal behavior and on the secretory pattern of intrauterine glycodelin at the midcycle of ovulatory women. *Study Design*: Thirty healthy sterilized women with normal ovarian function were studied during one control untreated cycle and one LNG-treated cycle. In the treated cycle, each woman received two doses of 0.75 mg of LNG twelve hours apart during the preovulatory phase approximately two days before the LH surge. Daily follicle development recordings were performed until follicle rupture was observed, and serum glycodelin, LH, estradiol, estrone, and progesterone were measured as well. In addition, glycodelin concentrations were assayed in uterine flushing obtained on Days LH+1 and LH+12. *Results*: LNG did not modify follicle rupture in twenty of thirty women. In spite of ovulatory progesterone and the occurrence of follicle rupture in these women, luteal phase length was significantly decreased, as well as the serum concentrations of LH, estradiol, and estrone in the periovulatory phase. Glycodelin in serum and uterine flushings was significantly elevated in the periovulatory phase when compared to control cycles. *Conclusions*: LNG taken at the dose used in emergency contraception before the LH surge increased prematurely serum and intrauterine concentrations of glycodelin at the time of ovulation. Since there are well established glycodelin inhibitory effects upon fertilization, these results may represent an additional action of LNG in situations where the intervention did not interfere with ovulation.

Volume 83, Number 1
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Trends in the Use of Contraceptive Methods and Voluntary Interruption of Pregnancy in the Spanish Population during 1997–2007

J. L. Dueñas et al.

Background: This study was designed to acquire information about the use of contraceptive methods in order to reduce the number of elective abortions. *Study Design*: Since 1997, representative samples of Spanish women of childbearing potential (fifteen to forty-nine years) have been surveyed by the Daphne Team every two years to gather data of contraceptive methods used. *Results*: During the study period, 1997 to 2007, the overall use of contraceptive methods increased from 49.1 to 79.9 percent. The most commonly used method was the condom (an increase from 21 to 38.8 percent), followed by the pill (an increase from 14.2 to 20.3 percent). Female sterilization and intrauterine devices decreased slightly and were used by less than 5 percent of women in 2007. The elective abortion rate increased from 5.52 to 11.49 per 1,000 women. *Conclusions*: The factors responsible for the increased rate of elective abortion need further investigation.

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March 2011

Ectopic Pregnancy after Levonorgestrel Emergency Contraception

Z. Kozkinszky, R. T. Bakken, and M. Lieng

Background: Although the possibility of ectopic pregnancy after intake of levonorgestrel (LNG) as an emergency contraceptive [EC] pill is well-known, the causality has not been well established. *Case*: A twenty-seven-year-old nulliparous woman with regular menstrual periods took 1.5 mg LNG-EC midcyclic five hours after an unprotected intercourse. She had prolonged vaginal bleeding at the expected time. She consulted the general practitioner because of continuous vaginal bleeding for four weeks and lower abdominal pain. The pregnancy test was positive, and her symptoms and clinical findings suggested an ectopic pregnancy. At emergency surgery, she was found to have a left tubal pregnancy. *Conclusion*: The possible role of 1.5 mg LNG-EC in causing ectopic pregnancy is discussed. A high serum LNG concentration decreases ciliary activity and tube motility, but further epidemiological studies are necessary to establish the risk of ectopic pregnancy following intake of LNG-EC.

Nature

Volume 469, Number 7328
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Telomerase Reactivation Reverses Tissue Degeneration in Aged Telomerase-Deficient Mice

M. Jaskelioff et al.

An ageing world population has fuelled interest in regenerative remedies that may stem declining organ function and maintain fitness. Unanswered is whether elimination of intrinsic instigators driving age-associated degeneration can reverse, as opposed to simply arrest, various afflictions of the aged. Such instigators include progressively damaged genomes. Telomerase-deficient mice have served as a model system to study the adverse cellular and organismal consequences of wide-spread endogenous DNA damage signaling activation in vivo. Telomere loss and uncapping provokes progressive tissue atrophy, stem cell depletion, organ system failure, and impaired tissue injury responses. Here, the authors sought to determine whether entrenched multi-system degeneration in adult mice with severe telomere dysfunction can be halted or possibly reversed by reactivation of endogenous telomerase activity. To this end, the authors engineered a knock-in allele encoding a 4-hydroxytamoxifen (4-OHT)-inducible telomerase reverse transcriptase-oestrogen receptor (TERT-ER) under transcriptional control of the endogenous TERT promoter. Homozygous TERT-ER mice have short dysfunctional telomeres and sustain

increased DNA damage signaling and classical degenerative phenotypes upon successive generational matings and advancing age. Telomerase reactivation in such late generation TERT-ER mice extends telomeres, reduces DNA damage signaling and associated cellular checkpoint responses, allows resumption of proliferation in quiescent cultures, and eliminates degenerative phenotypes across multiple organs including testes, spleens, and intestines. Notably, somatic telomerase reactivation reversed neurodegeneration with restoration of proliferating Sox2(+) neural progenitors, Dcx(+) newborn neurons, and Olig2(+) oligodendrocyte populations. Consistent with the integral role of subventricular zone neural progenitors in generation and maintenance of olfactory bulb interneurons, this wave of telomerase-dependent neurogenesis resulted in alleviation of hyposmia and recovery of innate olfactory avoidance responses. Accumulating evidence implicating telomere damage as a driver of age-associated organ decline and disease risk and the marked reversal of systemic degenerative phenotypes in adult mice observed here support the development of regenerative strategies designed to restore telomere integrity.

Volume 470, Number 7332
February 3, 2011

Directed Differentiation of Human Pluripotent Stem Cells into Intestinal Tissue In Vitro

J. R. Spence et al.

Studies in embryonic development have guided successful efforts to direct the differentiation of human embryonic and induced pluripotent stem (iPS) cells into specific organ cell types in vitro. For example, human iPS cells have been differentiated into monolayer cultures of liver hepatocytes and pancreatic endocrine cells that have therapeutic efficacy in animal models of liver disease and diabetes, respectively. However, the generation of complex three-dimensional organ tissues in vitro remains a major challenge for translational studies. Here the authors establish a robust and efficient process to direct the differentiation of human iPS cells into intestinal tissue in vitro using a temporal series of growth factor manipulations to mimic embryonic intestinal development. This involved activin-induced definitive endoderm formation, FGF/Wnt-induced posterior endoderm pattering, hindgut specification and morphogenesis, and a pro-intestinal culture system to promote intestinal growth, morphogenesis, and cytodifferentiation. The resulting three-dimensional intestinal 'organoids' consisted of a polarized, columnar epithelium that was patterned into villus-like structures and crypt-like proliferative zones that expressed intestinal stem cell markers. The epithelium contained functional enterocytes, as well as goblet, Paneth and enteroendocrine cells. Using this culture system as a model to study human intestinal development, the authors identified that the combined activity of WNT3A and FGF4 is required for hindgut specification whereas FGF4 alone is sufficient to promote hindgut morphogenesis. Their data indicate that human intestinal stem cells form de novo during development. They also determined that NEUROG3, a pro-endocrine transcription factor that is mutated in enteric anendocrinosis, is both necessary and sufficient for human enteroendocrine cell development in vitro. iPS cell-derived human intestinal tissue should allow for unprecedented studies of human intestinal development and disease.

Volume 471, Number 7336
March 3, 2011

Somatic Coding Mutations in Human Induced Pluripotent Stem Cells

A. Gore et al.

Defined transcription factors can induce epigenetic reprogramming of adult mammalian cells into induced pluripotent stem cells. Although DNA factors are integrated during some reprogramming methods, it is unknown whether the genome remains unchanged at the single nucleotide level. Here the authors show that twenty-two human induced pluripotent stem (iPS) cell lines reprogrammed using five different methods each contained an

average of five protein-coding point mutations in the regions sampled (an estimated six protein-coding point mutations per exome). The majority of these mutations were non-synonymous, nonsense or splice variants, and were enriched in genes mutated or having causative effects in cancers. At least half of these reprogramming-associated mutations pre-existed in fibroblast progenitors at low frequencies, whereas the rest occurred during or after reprogramming. Thus, human iPS cells acquire genetic modifications in addition to epigenetic modifications. Extensive genetic screening should become a standard procedure to ensure human iPS cell safety before clinical use.

Copy Number Variation and Selection during Reprogramming to Pluripotency

S. M. Hussein et al.

The mechanisms underlying the low efficiency of reprogramming somatic cells into induced pluripotent stem (iPS) cells are poorly understood. There is a clear need to study whether the reprogramming process itself compromises genomic integrity and, through this, the efficiency of iPS cell establishment. Using a high-resolution single nucleotide polymorphism array, the authors compared copy number variations of different passages of human iPS cells with their fibroblast cell origins and with human embryonic stem cells. Here the authors show that significantly more copy number variations are present in early-passage human iPS cells than intermediate passage human iPS cells, fibroblasts or human embryonic cells. Most copy number variations are formed de novo and generate genetic mosaicism in early-passage human iPS cells. Most of these novel copy number variations rendered the affected cells at a selective disadvantage. Remarkably, expansion of human iPS cells in culture selects rapidly against mutated cells, driving the lines towards a genetic state resembling human embryonic stem cells.

Hotspots of Aberrant Epigenomic Reprogramming in Human Induced Pluripotent Stem Cells

R. Lister et al.

Induced pluripotent stem (iPS) cells offer immense potential for regenerative medicine and studies of disease and development. Somatic cell reprogramming involves epigenomic reconfiguration, conferring iPS cells with characteristics similar to embryonic stem cells. However, it remains unknown how complete the reestablishment of embryonic-stem-cell-like DNA methylation patterns is throughout the genome. Here the authors report the first whole-genome profiles of DNA methylation at single-base resolution in five human iPS cell lines, along with methylomes of embryonic stem cells, somatic cells, and differentiated iPS cells and embryonic cells. iPS cells show significant reprogramming variability, including somatic memory and aberrant reprogramming of DNA methylation. iPS cells share megabase-scale differentially methylated regions proximal to centromeres and telomeres that display incomplete reprogramming of non-CG methylation, and differences in CG methylation and histone modifications. Lastly, differentiation of iPS cells into trophoblast cells revealed that errors in reprogramming CG methylation are transmitted at a high frequency, providing an iPS cell reprogramming signature that is maintained after differentiation.

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March 17, 2011

Progesterone Activates the Principal Ca2+ Channel of Human Sperm

P. V. Lishko, I. L. Botchkina, and Y. Kirichok

Steroid hormone progesterone released by cumulus cells surrounding the egg is a potent stimulator of human spermatozoa. It attracts spermatozoa toward the egg and helps them penetrate the egg's protective vestments. Progesterone induces Ca(2+) influx into spermatozoa and triggers multiple Ca(2+)-dependent physiological responses essential

for successful fertilization, such as sperm hyperactivation, acrosome reaction and chemotaxis towards the egg. As an ovarian hormone, progesterone acts by regulating gene expression through a well-characterized progesterone nuclear receptor. However, the effect of progesterone on transcriptionally silent spermatozoa remains unexplained and is believed to be mediated by a specialized, non-genomic membrane progesterone receptor. The identity of this non-genomic progesterone receptor and the mechanism by which it causes Ca(2+) entry remain fundamental unresolved questions in human reproduction. Here the authors elucidate the mechanism of the non-genomic action of progesterone on human spermatozoa by identifying the Ca(2+) channel activated by progesterone. By applying the patch-clamp technique to mature human spermatozoa, the authors found that nanomolar concentrations of progesterone dramatically potentiate CatSper, a pH-dependent Ca(2+) channel of the sperm flagellum. They demonstrate that human CatSper is synergistically activated by elevation of intracellular pH and extracellular progesterone. Interestingly, human CatSper can be further potentiated by prostaglandins, but apparently through a binding site other than that of progesterone. Because the authors' experimental conditions did not support second messenger signaling, CatSper or a directly associated protein serves as the elusive non-genomic progesterone receptor of sperm. Given that the CatSper-associated progesterone receptor is sperm specific and structurally different from the genomic progesterone receptor, it represents a promising target for the development of a new class of non-hormonal contraceptives.

Nature Biotechnology

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March 2011

A Functionally Characterized Test Set of Human Induced Pluripotent Stem Cells

G. L. Boulting et al.

Human induced pluripotent stem (iPS) cells present exciting opportunities for studying development and for in vitro disease modeling. However, reported variability in the behavior of iPS cells has called their utility into question. The authors established a test set of sixteen iPS cell lines from seven individuals of varying age, sex, and health status, and extensively characterized the lines with respect to pluripotency and the ability to terminally differentiate. Under standardized procedures in two independent laboratories, thirteen of the iPS cell lines gave rise to functional motor neurons with a range of efficiencies similar to that of human embryonic stem cells. Although three iPS cell lines were resistant to neural differentiation, early neuralization rescued their performance. Therefore, all sixteen iPS cell lines passed a stringent test of differentiation capacity despite variations in karyotype and in the expression of early pluripotency markers and transgenes. This iPS cell and embryonic stem cell test set is a robust resource for those interested in the basic biology of stem cells and their applications.

Generation of Anterior Foregut Endoderm from Human Embryonic and Induced Pluripotent Stem Cells

M. D. Green et al.

Directed differentiation of human embryonic stem cells and human induced pluripotent stem cells captures in vivo developmental pathways for specifying lineages in vitro, thus avoiding perturbation of the genome with exogenous genetic material. Thus far, derivation of endodermal lineages has focused predominantly on hepatocytes, pancreatic endocrine cells, and intestinal cells. The ability to differentiate pluripotent cells into anterior foregut endoderm (AFE) derivatives would expand their utility for cell therapy and basic research to tissues important for immune function, such as the thymus; for metabolism, such as thyroid and parathyroid; and for respiratory function, such as trachea and lung. The authors find that dual inhibition of transforming growth factor -β and bone morphogenic protein signaling after specification of definitive endoderm from pluripotent cells results in

a highly enriched AFE population that is competent to be patterned along dorsoventral and anteroposterior axes. These findings provide an approach for the generation of AFE derivatives.

New England Journal of Medicine

Volume 364, Number 4
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Induced First-Trimester Abortion and Risk of Mental Disorder

T. Munk-Olsen et al.

Background: Concern has been expressed about potential harm to women's mental health in association with having an induced abortion, but it remains unclear whether induced abortion is associated with an increased risk of subsequent psychiatric problems. *Methods*: The authors conducted a population-based cohort study that involved linking information from the Danish Civil Registration system to the Danish Psychiatric Central Register and the Danish National Register of Patients. The information consisted of data for girls and women with no record of mental disorders during the 1995 to 2007 period who had a first-trimester induced abortion or a first childbirth during that period. The authors estimated the rates of first-time psychiatric contact (an inpatient admission or outpatient visit) for any type of mental disorder within the twelve months after the abortion or childbirth as compared with the nine-month period preceding the event. *Results*: The incidence rates of first psychiatric contact per thousand person-years among girls and women who had a first abortion were 14.6 (95% CI, 13.7 to 15.6) before abortion and 15.2 (95% CI, 14.4 to 16.1) after abortion. The corresponding rates among girls and women who had a first childbirth were 3.9 (95% CI, 3.7 to 4.2) before delivery and 6.7 (95% CI, 6.4 to 7.0) post partum. The relative risk of a psychiatric contact did not differ significantly after abortion as compared with before abortion ($P = 0.19$) but did increase after childbirth as compared with before childbirth ($P < 0.001$). *Conclusions*: The finding that the incidence rate of psychiatric contact was similar before and after a first-trimester abortion does not support the hypothesis that there is an increased risk of mental disorders after a first-trimester induced abortion.

PNAS: Proceedings of the National Academy of Sciences USA

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Understanding Current Causes of Women's Underrepresentation in Science

S.J. Ceci and W.M. Williams

Explanations for women's underrepresentation in math-intensive fields of science often focus on sex discrimination in grant and manuscript reviewing, interviewing, and hiring. Claims that women scientists suffer discrimination in these arenas rest on a set of studies undergirding policies and programs aimed at remediation. More recent and robust empiricism, however, fails to support assertions of discrimination in these domains. To better understand women's underrepresentation in math-intensive fields and its causes, the authors reprise claims of discrimination and their evidentiary bases. Based on a review of the past twenty years of data, the authors suggest that some of these claims are no longer valid and, if uncritically accepted as current causes of women's lack of progress, can delay or prevent understanding of contemporary determinants of women's underrepresentation. The authors conclude that differential gendered outcomes in the real world result from differences in resources attributable to choices, whether free or constrained, and that such choices could be influenced and better informed through education if resources were so directed. Thus, the ongoing focus on sex discrimination in reviewing, interviewing, and hiring represents costly,

misplaced effort: Society is engaged in the present in solving problems of the past, rather than in addressing meaningful limitations deterring women's participation in science, technology, engineering, and mathematics careers today. Addressing today's causes of underrepresentation requires focusing on education and policy changes that will make institutions responsive to differing biological realities of the sexes. Finally, the authors suggest potential avenues of intervention to increase gender fairness that accord with current, as opposed to historical, findings.

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Paternal MHC Expression on Mouse Trophoblast Affects Uterine Vascularization and Fetal Growth

Z. Madeja et al.

The mammalian fetus represents a semiallograft within the maternal uterus yet is not rejected. This situation is particularly pronounced in species with a hemochorial type of placentation, such as humans and rodents, where maternal tissues and blood are in direct contact with fetal trophoblast and thus potentially with paternal antigens. The main polymorphic antigens responsible for graft rejection are MHC antigens. In humans the trophoblast cells invading into the decidua have a unique pattern of MHC class I expression characterized by both classical (HLA-C) and nonclassical (HLA-G and HLA-E) molecules. Whether such an unusual MHC repertoire on the surface of trophoblast is a conserved feature between species with hemochorial placentation has not been resolved. Here the authors demonstrate, using a range of methods, that C57BL/6 mouse trophoblast predominantly expresses only one MHC class I antigen, H2-K, at the cell surface of giant cells but lacks expression of nonclassical MHC molecules. Antigenic disparity between parental MHCs affects trophoblast-induced transformation of the uterine vasculature and, consequently, placental and fetal growth. Maternal uterine blood vessels were more dilated, allowing for increased blood supply, in certain combinations of maternal and paternal MHC haplotypes, and these allogeneic fetuses and placentas were heavier at term compared with syngeneic controls. Thus, maternal–fetal immune interactions are instrumental to optimize reproductive success. This cross-talk has important implications for human disorders of pregnancy, such as preeclampsia and fetal growth restriction.

Science

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The Antiproliferative Action of Progesterone in Uterine Epithelium Is Mediated by Hand2

Q. Li et al.

During pregnancy, progesterone inhibits the growth-promoting actions of estrogen in the uterus. However, the mechanism for this is not clear. The attenuation of estrogen-mediated proliferation of the uterine epithelium by progesterone is a prerequisite for successful implantation. The authors' study reveals that progesterone-induced expression of the basic helix-loop-helix transcription factor Hand2 in the uterine stroma suppresses the production of several fibroblast growth factors that act as paracrine mediators of mitogenic effects of estrogen on the epithelium. In mouse uteri lacking Hand2, continued induction of these fibroblast growth factors in the stroma maintains epithelial proliferation and stimulates estrogen-induced pathways, resulting in impaired implantation. Thus, Hand2 is a critical regulator of the uterine stromal-epithelial communication that directs proper steroid regulation conducive for the establishment of pregnancy.