CHAPTER 6

IMPLANTATION

Fatma OZDEMIR, I. Ipek MUDERRIS

What are the basic principles of embryo implantation in human?

For successful implantation, a viable blastocyst and an effective communication with blastocyst and a receptive endometrium are required. It's a higly coordinated, complex and continuing process. The complex molecular and physical interaction between the embryo and the host endometrium is a requirement of this process (1). Embryo implantation in humans involves sequential steps for apposition, adhesion and invasion of an implantation-component blastocyst into a hormonaly prepared receptive endometrium (2,3). Embryo should be well developed and be conducive to implantation. The endometrium needs to become a receptive state for implantation to occur (4).

What is the clinical importance of receptive endometrium in implantation?

Uterine receptivity refers to a structure for allowing and facilitating the implantation of conception. Ovarian hormonesplays a very important role in these events (5). The development of the embryo into the blastocyst stage suitable for implantation and the preparation of the endometrium for implantation should take place concurrently and synchrony (5). When the endometriumis receptive for the blastocyst the embryo must be atthe blastocyst stage and has to be in the uterus. If the blastocyst is ready for implantation but the endometrium is not yet in the receptivity phase, the blastocyst may wait for endometrial receptivity. If the endometrium is in receptivity phase and ready for implantation but the blastocyst is not suitable for implantation endometrium can not wait for blastocyst to be ready (6-7). "Window of implantation" is the time that the endometrium is receptive for the implantation of blastocyst. After the end of the receptive perioduterus becomes unresponsive, refractory, insensitive, and even toxicto the blastocyst and as a result the receptivity of endometrium is lost (8).

How the invasive extravillous trophoblasts "know" when to stop?

In the decidualization process, some protective mechanisms are working which limit excessive trophoblast invasion and thus prevent pathologies such as placenta accrete (64). The invasion process is tightly regulated. Decidua, myometrium and decidual natural killer cells play a role in guiding and limiting this process. To moderate the depth of invasion of the invasive extravillous trophoblast, decidual stromal cells express tissue inhibitors of matrix metalloproteinases and plasminogen activator inhibitors. To inhibit direct invasion of the spiral arteries decidual natural killer cells produce and release chemoattractants (65,66).

References

1. Guiying N, Dimitriadis E. (2019) Moleculer and Cellular Basis of Human Embryo İmplantation, Ed: Gabor Kovacs, Lois Salamonsen How to Prepare the Endometrium to Maximize İmplantation Rates and IVF Success, (pp:10-17), Cambrigde University Press
2. James JL, Carter AM, Chamley LW. Human placentation from nidation to 5 weeks of gestation. Part I: What do we know about formative placental development following implantation? Placenta 33 (2012) 327-334
3. Salamonsen LA, Nie G, Hannan N, Dimitriadis E. Society for Reproductive Biology Founders' Lecture 2009. Preparing fertile soil: the importance of endometrial receptivity, Reproduction, Fertility and Development 21(7) 923-934
4. Evans J, salamonsen LA, Winship A et all, Fertile ground: human endometrial programming and lessons in healt and disease. Nat Rev endocrinol 2016;12:654-667
5. Yoshinaga K, (1988) Uterine receptivity for blastocyst implantation, İn Vitro Fertilization and Other Asisted Reproduction. (pp:424-431) Annals of the Newyork Academy of Sciences.
6. Chang M. C. 1950. Development and fate of transferred rabbit ova or blastocysts in relation to the ovulation time of recipients. J. Exp. Zool. 114 197-226.
7. Dickmann Z, Noyes RW, The Fate of Ova Transferred into the Uterus of the Rat. J Reprod Fertil (1960) 1; 197-212
8. Doyle LL, Gates AH, Noyes RW.. Asynchronous transfer of mouse ova.Fertil. Steril. (1963)14: 215-225.
9. Hodgen G. D. 1983. Surrogate embryo transfer combined with estrogen-progesterone therapy in monkeys. Implantation, gestation, and delivery without ovaries. J. Am. Med. Assoc. 250(16): 2167-21 71.
10. Lejeune B, Dehou MF, Leroy F. Tentative extrapolation of animal data to human implantation. Ann. N. Y. Acad. Sci.(1986) 476: 63-74.
11. Speroff, Leon, and Marc A. Fritz, eds. Clinical gynecologic endocrinology and infertility. lippincott Williams & wilkins, 2005.
12. Yoshinaga K, (1988) Uterine receptivity for blastocyst implantation, İn Vitro Fertilization and Other Asisted Reproduction. (pp:424-431) Annals of the Newyork Academy of Sciences.
13. Cha J, Sun X, Dey SK. Mechanisms of implantation: strategies for successful pregnancy. Nature Medicine volume 18, pages1754–1767(2012)
14. Yoshinaga K, (1988) Uterine receptivity for blastocyst implantation, İn Vitro Fertilization and Other Asisted Reproduction. (pp:424-431) Annals of the Newyork Academy of Sciences.

15. Hess, A.P., Nayak, N.R. & Giudice, L.C. Oviduct and endometrium: cyclic changes in the primate oviduct and endometrium. in. Knobil and Neill's Physiology of Reproduction, Vol. 1 (ed. Neill, J.D.) 337–381 (Elsevier Academic Press, 2006).
16. Daikoku, T.Cha J, Sun X, et al. Conditional deletion of MSX homeobox genes in the uterus inhibits blastocyst implantation by altering uterine receptivity. Dev. Cell (2011).21, 1014–1024
17. Ma W, Song H, Das S, et all. PNAS March 4, 2003 100 (5) 2963-2968;Estrogen is a critical determinant that specifies the duration of the window of uterine receptivity for implantation
18. Lydon JP, DeMayo FJ, Funk CR, et al. Mice lacking progesterone receptor exhibit pleiotropic reproductive abnormalities. Genes Dev. 1995;9(18):2266-2278.
19. Dvorak, H. F., Nagy, J. A., Feng, D., Brown, L. F., and Dvorak, A. M. (1999) in Current Topics in Microbiology and Immunology. Vascular Growth Factors and Angiogenesis (Claesson-Welsh, L., ed) Vol. 237, pp. 97–132, SpringerVerlag, Berlin
20. Ferrara, N. (1997) Eur. J. Cancer 32A, 2413–2422
21. Carmeliet, P., Ferreira, V., Breier, G, et all. Nature (1996) 380, 435–439
22. Shalaby F, Rossant J, Yamaguchi T, et all. Failure of blood-island formation and vasculogenesis in Flk-1-deficient mice (1995) Nature 376, 62–66
23. Suri, C, Jones, P F, Patan S, et all. Requisite Role of Angiopoietin-1, a Ligand for the TIE2 Receptor, during Embryonic Angiogenesis (1996) Cell 87, 1171–1180
24. Sato TN., Tozawa Y, Deutsch U, et all. Distinct roles of the receptor tyrosine kinases Tie-1 and Tie-2 in blood vessel formation (1995) Nature 376, 70–74
25. Matsumoto H, Ma W, Daikoku T, Cyclooxygenase-2 Differentially Directs Uterine Angiogenesis during Implantation in Mice (2002) The Journal of Biological Chemistry 277, 29260-29267.
26. Matsumoto H, Ma W, Daikoku T, Cyclooxygenase-2 Differentially Directs Uterine Angiogenesis during Implantation in Mice (2002) The Journal of Biological Chemistry 277, 29260-29267.
27. Lim H, Gupta RA, Ma W, et all. Cyclo-oxygenase-2-derived prostacyclin mediates embryo implantation in the mouse via PPARδ (1999) Genes Dev. 13, 1561–1574
28. Lim H, Paria BC, Das SK, Multiple Female Reproductive Failures in Cyclooxygenase 2–Deficient Mice (1997) Cell 91, 197–208
29. Dinchuk JE, Car BD, Focht RJ, et all Renal abnormalities and an altered inflammatory response in mice lacking cyclooxygenase II (1995) Nature 378, 406–409
30. Langenbach R, Morham SG, Tiano HF et all. Prostaglandin synthase 1 gene disruption in mice reduces arachidonic acid-induced inflammation and indomethacin-induced gastric ulceration (1995) Cell 83, 483–492
31. Bhatt H, Brunet LJ, stewart CL. Uterine expression of leukemia inhibitory factor coincides with the onset of blastocyst implantation. PNAS December 15, 1991 88 (24) 11408-11412
32. Song H, Lim H, Das SK., et all. Dysregulation of EGF Family of Growth Factors and COX-2 in the Uterus during the Preattachment and Attachment Reactions of the Blastocyst with the Luminal Epithelium Correlates with Implantation Failure in LIF- Deficient Mice (2000) Mol. Endocrinol. 14, 1147–1161.
33. Das SK, Chakraborty I, Paria BC.,et all. Amphiregulin is an implantation-specific and progesterone-regulated gene in the mouse uterus. (1995) Mol. Endocrinol. 9, 691–705.
34. Benson GV, Lim H, Paria BC,et all. Mechanisms of reduced fertility in Hoxa-10 mutant mice: uterine homeosis and loss of maternal Hoxa-10 expression. (1996) Development 122, 2687–2696.
35. Stewar, CL, Kasper P, Brunet L, et all. Blastocyst implantation depends on maternal expression of leukemia inhibitory factor.(1992) Nature 359, 76–79.
36. Lim H, Ma L, Ma WG, et all. Hoxa-10 regulates uterine stromal cell responsiveness to progesterone during implantation and decidualization in the mouse. (1999) Mol. Endocrinol. 13, 1005–1017

37. Paria BC, Reese J, Das SK et all. Deciphering the cross-talk of implantation: advances and challenges. (2002) Science 296, 2185–2188.
38. Niakan KK, Han J, Pedersen RA, et all. Human pre-implantation embryo development. Development. 2012 Mar;139(5):829-41
39. Baker TG. Gametogenesis. European Journal of Endocrinology, 1972, 71.1_Suppl: S18-S41.
40. Spindle, Akiko I., and Roger A. Pedersen. "Hatching, attachment, and outgrowth of mouse blastocysts in vitro: fixed nitrogen requirements." Journal of Experimental Zoology 186.3 (1973): 305-318.
41. Gwatkin, R. B. L., and D. T. Williams. "Receptor activity of the hamster and mouse solubilized zona pellucida before and after the zona reaction." Reproduction 49.1 (1977): 55-59.
42. Carson, Daniel D., et al. "Embryo implantation." Developmental biology 223.2 (2000): 217-237.
43. Lentz, Gretchen M., et al. Comprehensive gynecology e-book. Elsevier Health Sciences, 2012.
44. Guiying N, Dimitriadis E. (2019) Moleculer and Cellular Basis of Human Embryo İmplantation, Ed: Gabor Kovacs ,Lois Salamonsen How to Prepare the Endometrium to Maximize İmplantation Rates and IVF Success, (pp:10-17), Cambrigde University Press
45. Brosens, Jan J., Robert Pijnenborg, and Ivo A. Brosens. "The myometrial junctional zone spiral arteries in normal and abnormal pregnancies: a review of the literature." American journal of obstetrics and gynecology 187.5 (2002): 1416-1423.
46. Lentz, Gretchen M., et al. Comprehensive gynecology e-book. Elsevier Health Sciences, 2012.
47. Chiu et al., 2014. Chiu P., Lam K., Wong R., et al: The identity of zona pellucida receptor on spermatozoa: an unresolved issue in developmental biology. Semin Cell Dev Biol 2014; 30: pp. 86-95
48. Speroff, Leon, and Marc A. Fritz, eds. Clinical gynecologic endocrinology and infertility. lippincott Williams & wilkins, 2005.
49. Carson, Daniel D., et al. "Embryo implantation." Developmental biology 223.2 (2000): 217-237.
50. Parr, Margaret B., and Earl L. Parr. "The implantation reaction." Biology of the Uterus. Springer, Boston, MA, 1989. 233-277.
51. Speroff, Leon, and Marc A. Fritz, eds. Clinical gynecologic endocrinology and infertility. lippincott Williams & wilkins, 2005.
52. Cha J, Sun X, and Dey SK: Mechanisms of implantation: strategies for successful pregnancy. Nat Med 2012; 18: pp. 1754-1767
53. Tu Z, Ran H, Zhang S, et al: Molecular determinants of uterine receptivity. Int J Dev Biol 2014; 58: pp. 147-154
54. Lim HJ, and Dey SK: HB-EGF: a unique mediator of embryo-uterine interactions during implantation. Exp Cell Res 2009; 315: pp. 619-626
55. Stavreus-Evers A, Aghajanova L, Brismar H, et al: Co-existence of heparin-binding epidermal growth factor-like growth factor and pinopodes in human endometrium at the time of implantation. Mol Hum Reprod 2002; 8: pp. 765-769
56. Creasy, Robert K., et al. Creasy and Resnik's Maternal-Fetal Medicine: Principles and Practice E-Book. Elsevier Health Sciences, 2013.
57. Leach RE, Romero R, Kim YM, et al: Pre-eclampsia and expression of heparin-binding EGF-like growth factor. Lancet 2002; 360: pp. 1215-1219
58. Carson, Daniel D., et al. "Embryo implantation." Developmental biology 223.2 (2000): 217-237.
59. Speroff, Leon, and Marc A. Fritz, eds. Clinical gynecologic endocrinology and infertility. lippincott Williams & wilkins, 2005
60. Gellersen B, Brosens JJ, Cyclic Decidualization of the Human Endometrium in Reproductive Health and Failure. Endocrine Reviews 35: 851–905, 2014
61. Comprehensive Gynecology, Fertilization and Embryogenesis: Meiosis, Fertilization, Implantation, Embryonic Development, Sexual Differentiation, pages:1-21

62. Brosens et al., 2002. Brosens J.J., Pijnenborg R., and Brosens I.A.: The myometrial junctional zone spiral arteries in normal and abnormal pregnancies: a review of the literature. Am J Obstet Gynecol 2002; 187: pp. 1416-1423
63. Speroff, Leon, and Marc A. Fritz, eds. Clinical gynecologic endocrinology and infertility. lippincott Williams & wilkins, 2005
64. Gellersen B, Brosens JJ, Cyclic Decidualization of the Human Endometrium in Reproductive Health and Failure. Endocrine Reviews 35: 851–905, 2014
65. Le Bouteiller P: Human decidual NK cells: unique and tightly regulated effector functions in healthy and pathogen-infected pregnancies. Front Immunol 2013; 4: pp. 404
66. Creasy, Robert K., et al. Creasy and Resnik's Maternal-Fetal Medicine: Principles and Practice E-Book. Elsevier Health Sciences, 2013.