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Molecular Events Underlying Pregnancy-Induced Cardiomyopathy

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The etiology of cardiomyopathy in pregnant women remains unclear. In this issue, Hilfiker-Kleiner et al. (2007) report that a reduction in STAT3 and a concomitant increase in cathepsin D may be a cause of this disease. Cathepsin D generates an antiangiogenic cleavage product of the hormone prolactin. The authors show that an inhibitor of prolactin secretion may be useful in treating this disease.

Heart failure can occur in pregnant women or up to six months after the birth of the baby. This potentially fatal disorder is referred to as peripartum (or postpartum) cardiomyopathy. The incidence varies according to country of origin, but in the United States, it occurs in about 1000–1300 women per year (see Pearson et al., 2000), with mortality rates between 18%–56%. By definition, it strikes women with no prior history of heart disease, and surviving women may suffer long-term debilitating effects and may require a heart transplant. Thus far, there has been little insight into the causes of pregnancy-induced cardiomyopathy. Potential causes include inflammation of the myocardium (myocarditis) or activation of cytokines from stress. A mouse model of dilated cardiomyopathy—in which there is overexpression of the α subunit of the protein Gq in cardiac tissue—exhibits pregnancy-induced cardiomyopathy (Hayakawa et al., 2003). However, it does not seem that this overexpression occurs in women with peripartum cardiomyopathy. In this issue of *Cell*, Hilfiker-Kleiner et al. (2007) show in female mice and pregnant women a relationship between the transcription factor STAT3, an antiangiogenic cleavage product of prolactin and peripartum cardiomyopathy.

During a normal pregnancy, women experience cardiac hypertrophy and reduced relaxation or diastolic function. But in most women this hypertrophy regresses, and function returns to normal following childbirth. Pregnancy-induced hypertrophy has been thought to be similar to the cardiac growth that occurs in response to exercise, but there has not been extensive investigation of the pathways leading to pregnancy-induced cardiac hypertrophy. Additionally, although many pathways have been implicated in the formation of new blood vessels (angiogenesis), little is known about angiogenesis in the heart during pregnancy. Recently, STAT3 was shown to be critical for cardiac angiogenesis (Hilfiker-Kleiner et al., 2005). STAT3, a DNA binding protein that is activated by the interleukin (IL)-6 family of cytokines, has been implicated in a wide variety of biological processes, including inflammation, angiogenesis, and cardiac hypertrophy. Deletion of STAT3 in mice results in embryonic lethality, but deletion in heart tissue alone results in loss of capillary density with age. In their new study, Hilfiker-Kleiner et al. (2007) found that female mice lacking STAT3 in the heart develop normal pregnancy-induced cardiac hypertrophy accompanied by a normal increase in angiogenesis. However, these mice develop pregnancy-induced cardiomyopathy due to an inability to maintain the pregnancy-induced increase in capillary density. STAT3 has been shown to be cardioprotective by reducing the production of reactive oxygen species (Negoro et al., 2001). Reactive oxygen species can induce the expression of a wide variety of genes, including cathepsin D. The authors confirmed this role for STAT3, as mice that lacked STAT3 in heart tissue had elevated reactive oxygen species and elevated levels of cathepsin D. An antiangiogenic cleavage product of prolactin generated by cathepsin D was found in women with peripartum cardiomyopathy. Furthermore, the authors demonstrated that treatment of a cohort of mice and six women (in a preliminary clinical trial) exhibiting peripartum cardiomyopathy with a drug that blocks the secretion of prolactin (bromocriptine) reduced mortality.

Where does prolactin fit into these observations? Prolactin is a hormone made by the pituitary and is produced in both men and women. The amount of circulating prolactin increases late in pregnancy and is known to activate STAT3 (Cataldo et al., 2000). Prolactin has been implicated in >300 biological processes, including milk production, immune regulation, and reproduction. Some of this diversity in function may be due to the multiple forms of prolactin, which have distinct activities. For example, full-length prolactin is thought to have proangiogenic activities, whereas the 16 kDa cleavage product has potent antiangiogenic and proapoptotic activities (Corbacho et al., 2002). As Hilfiker-Kleiner et al. (2007) demonstrate, the 16 kDa cleavage product is clearly a major contributor to pregnancy-induced cardiomyopathy. However, the 16 kDa form of prolactin has

been shown to inhibit tumor growth via its antiangiogenic activity. Paradoxically, expression of cathepsin D (which cleaves prolactin) is positively associated with tumor metastasis (see Corbacho et al., 2002). Therefore, inhibiting prolactin secretion may have a variety of consequences. However, if bromocriptine were used to treat peripartum cardiomyopathy, it would only be administered for a short period of time and therefore may not affect long-term health.

An obvious question that arises from this study is, will all or most women with peripartum cardiomyopathy have an etiology that involves 16 kDa prolactin? There is a single report of peripartum cardiomyopathy in the literature in a woman who had elevated levels of prolactin, but that was observed over 20 years ago (Matharu and Oelbaum, 1984). In the current study (Hilfiker-Kleiner et al., 2007), the 16 kDa form of prolactin was found in serum from three out of five lactating mothers with pregnancy-induced cardiomyopathy, and there was a marked decrease in STAT3 and increase in cathepsin D in all five samples of heart tissue examined. Although these findings are interesting, further studies with a larger number of patients are certainly required.

How specific are the observations of Hilfiker-Kleiner et al. (2007) to pregnancy-induced cardiomyopathy? Although prolactin may be specific to pregnancy, other components discussed here seem likely to be involved in other forms of cardiac hypertrophy and heart failure. Upregulation of cathepsin D has been demonstrated in a hamster model of cardiac failure but is not altered in exercise-induced cardiac hypertrophy (Salminen and Vihko, 1983). This observation is consistent with cathepsin D activation being a general marker in different cardiac pathologies. However, *activation* of STAT3 has been observed in hearts of patients with dilated cardiomyopathy (Ng et al., 2003), suggesting that a reduction of STAT3 may be a more specific marker of pregnancy-induced cardiomyopathy. It will be interesting to determine whether there are single nucleotide polymorphisms (SNPs) in the human genome that reduce the levels of STAT3 in the heart and if those individuals carrying such SNPs exhibit a general deficiency in cardiac capillary density.

There are many animal models of cardiac hypertrophy and heart failure that will need to be examined to see whether they have the same molecular mechanisms as pregnancy-induced cardiomyopathy. Such studies will be an important addition to the intriguing results of Hilfiker-Kleiner et al. (2007) and the very encouraging data they have obtained with bromocriptine, a drug that has been used for a number of years to treat individuals with abnormally high levels of prolactin. Hopefully, a larger-scale clinical trial of bromocriptine to treat pregnancy-induced cardiomyopathy will be launched in the not-too-distant future. This will be of tremendous value both to women suffering from peripartum cardiomyopathy for the first time and to those who have survived a single bout of this disease and who have been counseled not to have additional pregnancies.

REFERENCES

Cataldo, L., Chen, N.Y., Yuan, Q., Li, W., Ramamoorthy, P., Wagner, T.E., Sticca, R.P., and Chen, W.Y. (2000). Int. J. Oncol. *17*, 1179–1185.

Corbacho, A.M., Martinez De La Escalera, G., and Clapp, C. (2002). J. Endocrinol. *173*, 219–238.

Hayakawa, Y., Chandra, M., Miao, W., Shirani, J., Brown, J.H., Dorn, G.W., 2nd, Armstrong, R.C., and Kitsis, R.N. (2003). Circulation *108*, 3036–3041.

Hilfiker-Kleiner, D., Limbourg, A., and Drexler, H. (2005). Trends Cardiovasc. Med. *15*, 152–157.

Hilfiker-Kleiner, D., Kaminski, K., Podewski, E., Bonda, T., Schaefer, A., Sliwa, K., Forster, O., Quint, A., Landmesser, U., Doerries, C., et al. (2007). Cell, this issue.

Matharu, G.S., and Oelbaum, M.H. (1984). Postgrad. Med. J. *60*, 49–51.

Negoro, S., Kunisada, K., Fujio, Y., Funamoto, M., Darville, M.I., Eizirik, D.L., Osugi, T., Izumi, M., Oshima, Y., Nakaoka, Y., et al. (2001). Circulation *104*, 979–981.

Ng, D.C., Court, N.W., dos Remedios, C.G., and Bogoyevitch, M.A. (2003). Cardiovasc. Res. *57*, 333–346.

Pearson, G.D., Veille, J.C., Rahimtoola, S., Hsia, J., Oakley, C.M., Hosenpud, J.D., Ansari, A., and Baughman, K.L. (2000). JAMA *283*, 1183–1188.

Salminen, A., and Vihko, V. (1983). Comp. Biochem. Physiol. B *76*, 93–95.