Gender influence on human EPCs

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Despite the influence of sex-gender has been widely studied in the physiology and pathology of the cardiovascular system (Mosca et al, 2011) is still great lack of knowledge regarding the risk factors, diagnosis, prognosis, events and drug response. The identification of sex-specific biomarker is relevant and could help to diagnose and predict cardiovascular events but the influence of sex-gender on new cardiovascular risk factors such as inflammation and endothelial dysfunction has been less investigated (Straface et al, 2010). Several evidences indicate that endothelial progenitor cells (EPCs) constitute an important endogenous system that maintains endothelial integrity and vascular homeostasis and their function (migration and capacity of colony formation) seems to be controlled by oestrogen being influenced by menstrual cycle, menopause (Fadini et al 2008, Hoetzer et al 2007) and by exposure to endocrine disruptors, as bisphenol A. However, it is not known whether the number and function of EPCs is influenced by sex-gender. Therefore, the aim of the study was to study the influence of sex-gender on human EPCs, which could also be a prognostic marker because changes in circulating EPCs can potentially reflect conditions of endothelial dysfunction .

Healthy young men and women with regular menstrual cycles were enrolled in the study. Participants were free of medications with the exception of OC for women. Circulating EPCs were isolated as CD34+ cells using a magnetic separation system and characterized according to Emanueli et al. (2007). EPCs were used for transwell migration assay using 10^{-9} M and $^{10-10}$ M 17β-estradiol and bisphenol A (BPA) 10^{-8} M as chemoattractants for 24 h at 37°C in 5% CO_2. Cells were analyzed on a fluorescence microscope and images were captured at 20X magnification. Male and female EPCs were also used to oestrogens receptors expression detection by Western blot.

Selected men and women didn't differ in age (26.9±5.3 years for women and 27.9±5.8 years for men) but as expected men had a higher body weight than women (80.5±12.7 vs 52.7± 7.6 respectively; $P<0.001$).

The basal migration of EPCs obtained from male and female donors did not diverge. However, when EPCs were incubated with 17β-estradiol a significant gender-related difference in EPC migration was seen. In female EPCs, physiological concentrations of 17β-estradiol (10^{-9} M and $^{10-10}$ M) significantly decreased the migratory activity near to 50% (calculated as percentage of migrated cells) when compared to controls. In male EPCs 17β-estradiol did not affect the migratory capacity of cells. We also observed that BPA reduced migration only in female EPCs. Finally, experiments conducted to understand which oestrogen receptor isoform mediate the 17β-estradiol effect on migration, using the antagonist of ER-beta, THC, showed that the effect is linked to ERβ. Moreover, it was observed that ERβ was similarly expressed in male and female EPCs while ERα presented an higher expression in female cells

This indicates that the inhibitory effect of 17β-estradiol on EPCs migration is mediated by ERα, which in our sample is little expressed in male cells, confirming the lack of action of 17β-estradiol on these cells than in the female counterpart

The primary new finding of the present study is that EPCs migratory activity is markedly lower in young healthy women compared with men, and this reduction is attributable to ERα. Functional differences in circulating EPCs may contribute to the gender-related disparity reported in endothelial function and cardiovascular events. The lower migratory ability of female EPCs could help to explain the higher prevalence of endothelial dysfunction in women.

Mosca et al. Circulation , 123:1243-1262; 2011
Straface et al. Fundam Clin Pharmacol, 24:665-74, 2010
Fadini et al. Arterioscler Thromb Vasc Biol, 28: 997-1004, 2008
Hoetzer et al. Am J Cardiol, 99:46-48, 2007
Emanueli et al. Br J Pharmacol, 150: 873-82, 2007