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REPRODUCTIVE ENDOCRINOLOGY

Hypoxia in endometrial repair

> Levels of HIF-1α were lower in women with heavy menstrual bleeding

New research shows that hypoxia occurs in the endometrium during menstruation, which stabilizes HIF-1α and therefore drives repair of the endometrium. These findings could lead to new therapies for women with heavy menstrual bleeding.

Around 1 in 5 women experience heavy menstrual bleeding, which can be debilitating. "Current treatments are rather non-specific and often fail or are associated with hormonal adverse effects," explains corresponding author Hilary Critchley (MRC Centre for Reproductive Health, The University of Edinburgh, UK). "This means that otherwise healthy women proceed to operations that lead to infertility, such as hysterectomy." To develop much-needed new therapies, Maybin, Critchley and colleagues used human tissue samples and a mouse model of simulated menstruation.

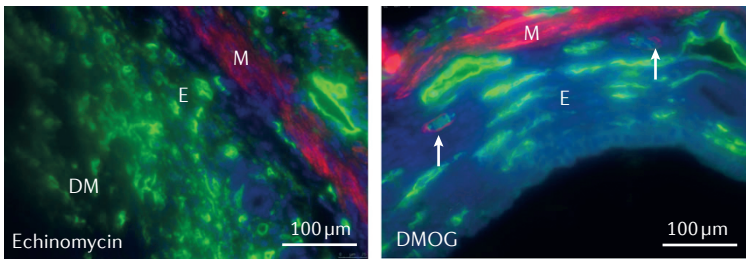
Hypoxia has long been thought to have a role at menses, so the researchers measured levels of HIF-1α (which mediates the cellular response to hypoxia and increases production of several repair factors) in endometrial biopsy samples from women with heavy menstrual bleeding and those with normal menstrual bleeding. Levels of HIF-1α were lower in women with heavy menstrual bleeding than in those with normal bleeding; menses also lasted longer in women with heavy menstrual bleeding. Furthermore, as there were no differences in HIF-1α transcript levels, the changes probably occurred after translation, such as through protein stabilization.

Next, ovariectomized mice were given oestrogen and progesterone, followed by removal of progesterone, to simulate menstruation. Hypoxia was detected in these mice during menstruation and was associated with increased levels of HIF-1α. When hypoxia was prevented from occurring, levels of HIF-1α were decreased and endometrial repair was delayed.

In addition, pharmacological inhibition of HIF-1α binding to hypoxia-response elements on target genes at menses by administration of echinomycin (to simulate the conditions in women with heavy menstrual bleeding) resulted in delayed endometrial repair in the mice. Interestingly, mice given dimethyloxalylglycine (which stabilizes HIF-1α) just before simulated menstruation showed more endometrial repair than mice given vehicle.

"These findings are an exciting first step towards a new, non-hormonal treatment for women with heavy menstrual bleeding," says Critchley. The researchers are now planning to investigate whether targeting the HIF pathway is an effective treatment strategy in these women.

Claire Greenhill



Stabilization of HIF-1α with dimethyloxalylglycine (DMOG; right) promotes endometrial repair in a mouse model of simulated menstruation; arrows show detection of the pericyte marker αSMA. Endothelial cells are abnormal and disorganized in mice treated with echinomycin, which inhibits HIF-1α (left). E, endometrium; DM, decidualized mass; M, myometrium. Reproduced with permission from Maybin, J. A. *et al. Nat. Commun.* **9**, 295 (2018), Macmillan Publishers Limited, CC BY 4.0.

ORIGINAL ARTICLE Maybin, J. A. *et al.* Hypoxia and hypoxia inducible factor-1α are required for normal endometrial repair during menstruation. *Nat. Commun.* **9**, 285 (2018)