75. Inhibition of the NLRP3 inflammasome by progesterone is attenuated by

abnormal autophagy induction in endometriotic cyst stromal cells: implications

for endometriosis

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Abstract

The NOD-like receptor pyrin domain containing 3 (NLRP3) inflammasome is a cytosolic

multi-protein complex that induces inflammation and is known to be regulated negatively by

autophagy. Previous studies reported an abnormal induction of autophagy linked to

progesterone resistance in human endometriotic cells. Therefore, an aberrant autophagy

induction response to progesterone might contribute to the altered inflammatory response

observed in endometriotic tissues. To evaluate this hypothesis, we elucidate whether

regulation of the NLRP3 inflammasome by ovarian steroids is mediated by autophagy in

human endometrial stromal cells (normal endometrial stromal cells (NESCs)) from patients

with uterine leiomyoma (presumed normal) and whether abnormal autophagy induction in

endometriotic cyst stromal cells (ECSCs) affects NLRP3 inflammasome-induced interleukin-

1β (IL-1β) production. Our results show that estrogen enhanced NLRP3 inflammasome

activation in NESCs, resulting in increased IL-1β production. Progesterone decreased NLRP3

inflammasome activity with an increase in autophagy induction in estrogen-treated NESCs.

Inhibition of NLRP3 inflammasome activity by progesterone was blocked by autophagy

inhibition. However, progesterone failed to change NLRP3 inflammasome activity and

autophagy induction in estrogen-treated ECSCs. In contrast, dienogest, a specific

progesterone receptor agonist, reduced NLRP3 inflammasome-mediated IL-1β production

through autophagy induction in ECSCs. Furthermore, autophagy induction was decreased and

NLRP3 inflammasome activity was increased in endometriotic tissues, which was reversed

by preoperative administration of dienogest. In conclusion, our results suggest that

progesterone inhibits NLRP3 inflammasome activation through autophagy in endometrial

stromal cells. However, this inhibitory effect is attenuated in endometriotic stromal cells due

to an aberrant autophagic response to progesterone, which could lead to an altered

inflammatory response in endometriosis.

Keywords: IL-1β; NLRP3 inflammasome; endometriosis; estrogen; progesterone