

# Autophagy in Spontaneous Miscarriage

## Abstract

The precise cause of some spontaneous miscarriages (SM) cannot always be identified. Autophagy, which is necessary for cellular survival in stressful situations, has also been linked to a number of illnesses. It has recently been hypothesized to be associated with SM. The precise mechanism, though, is still elusive. In actuality, trophoblast invasion, placentation, decidualization, enrichment, and infiltration of decidua immune cells (such as natural killer, macrophage, and T cells) are all crucial phases in the creation and maintenance of pregnancy. The discussion of these processes' respective upstream molecules and downstream effects of autophagy follows. Notably, autophagy also controls the communication between these cells at the maternal-fetal interface. Villi, decidual stromal cells, and peripheral blood mononuclear cells of SM patients exhibit aberrant autophagy, albeit the results are conflicting.

**Keywords:** Spontaneous miscarriage • Cellular survival • Trophoblast invasion • Placentation • Decidualization • Mononuclear cells

## Introduction

Though the precise definition is still debatable, Spontaneous Miscarriage (SM) refers to a natural pregnancy loss that occurs before 20 weeks of gestation. Given the recent rise in morbidity, it has generated a lot of social worry. Fetal chromosomal abnormalities, maternal infections, uterine structural malformations, endocrine problems, and immunological dysregulation are the main risk factors for SM. However, in a portion of instances, particularly those involving Recurrent Spontaneous Miscarriage (RSM), the underlying mechanisms are still unclear, necessitating urgent further study into the etiology, pathophysiology, and effective treatment options. In eukaryotic cells, macroautophagy/autophagy is a self-degradative cellular activity that ensures survival under adverse conditions such as an absence of energy or nutrients, inflammatory situations, oxidative stress, and endoplasmic reticulum stress. Additionally to maintaining cellular homeostasis, autophagy has been noted.

The five fundamental stages of autophagy are nucleation, elongation, maturation, fusion, and destruction. The phagophore, an isolating membrane that triggers autophagy, first engulfs internal cargo before expanding to create an autophagosome. Following this, the autophagosome matures by fusion with the lysosome, and the cargo is finally broken down for further recycling. When the Unc-51-Like Kinase 1 (ULK1) complex, made up of the

proteins focal adhesion kinase Family Interacting Protein of 200 kDa (FIP200), Atg13, and ULK1, is complete, autophagy is triggered. Mammalian target of rapamycin complex 1 (mTORC1) and 5' adenosine monophosphate-activated protein kinase (AMPK) control ULK1 complex negatively and positively, respectively, via directly inhibiting and boosting ULK activation, respectively. Phagophore development was followed by Atg5-Atg12 conjugation [1].

## Significance of autophagy in regulation of biological behaviour

**Cell survival and senescence:** Atg7 participates in autophagy, which prevents hypoxia-induced apoptosis and promotes placental trophoblast survival, although LC3 and Beclin-1 react differently to severe hypoxia (1% O<sub>2</sub>). Additionally, active autophagy limits cell death by p62-dependently degrading caspase-9. Overproduction of ROS activates NLRP1 inflammatory cells and encourages the release of IL-1 and CASP1. Autophagy and apoptosis are both increasing in the meantime. Silencing NLRP1 reduces IL-1, CASP1, and NLRP3 when exposed to ROS. After that, autophagy will take control to help the cell survive by increasing LC3-II, Beclin-1, Atg5, and Atg7 while lowering p62. On the other hand, inhibited autophagy will cause inflammasome expression. Therefore, autophagy is triggered by hypoxia-induced ROS to guarantee trophoblast survival. Nevertheless, Lee et al. reported autophagy as a trophoblast

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viability inhibitor with ROS buildup and ER stress. The intrinsic apoptosis that TNF-induced autophagy causes is mediated by Atg5, which can be prevented by resveratrol [2, 3].

**Invasion:** Conditional Atg7 deletion in rodent placental trophoblasts exhibits impaired invasion capacity and decreased MMP 2 and 9 levels. However, several researches have seen autophagy as a detrimental regulator for trophoblast invasion in human trophoblast cell lines. Inhibited trophoblast invasion in SM patients may result from aberrantly increased autophagy, claim Zhou et al.. In JAR cell line, active autophagy inhibits invasion; however, downregulated Beclin-1 somewhat alleviates this. By activating the NF- $\kappa$ B pathway, autophagy inhibition increases trophoblast invasion by upregulating MMP-2 and MMP-9 and downregulating TNF[4, 5]. The mitochondrion has been identified as a regulator of trophoblast migration and invasion as well as tumour cell migration and invasion. Human EVT<sub>s</sub> with invasion defects exhibit disrupted mitochondrial function with increased fission, decreased respiratory capacity, and decreased membrane potential. Recent research has focused on the role of autophagy in trophoblast invasion from the mitochondrial perspective. Aberrant autophagy may impair mitophagy (decreased PINK1) and disturb mitochondrion fission/fusion (decreased OPA1, MFN1, Drp1, and FIS1) in early human trophoblasts. Additionally, through BNIP3, an autophagy inducer, autophagy controls mitochondrial transmembrane potential, mitophagy, and mitochondrial biogenesis. It has been determined that the axis controlling mitochondrial biogenesis is SIRT1/AMPK/PGC-1. Human placental hydrolysate could repair mitochondrial damage in mouse myoblast cell line via autophagy [6, 7].

### Autophagy induction in spontaneous miscarriage

SM, which is defined by pregnancy loss before the 20th week, affects about 15% of pregnancies. RSM specifically refers to the incidence of three or more consecutive miscarriages, and more than half of cases have no clear etiology. Due to the abnormal expression of autophagy-related markers in SM/RSM, there is mounting evidence that autophagy plays a significant role. In addition to restricted Shh signalling pathways, RSM placentae had increased levels of LC3, LC3II/I, Atg5, and Beclin-1. Additionally, STBs from SM have been reported by Avagliano et

al. to have more autophagosomes and a higher density of LC3 labelling than STBs from healthy controls [8].

It's interesting to note that women who have previously experienced spontaneous pregnancy losses but have not given birth have higher peripheral blood mononuclear cell autophagy than women who have just conceived. However, there are several contradictions in this. Plasmacytoma Variant Translocation 1 (PVT1) is less common in the villi of RSM patients, according to research by Yang et al. In the HTR-8/SVneo cell line, PVT1 knockdown results in defective autophagy with elevated mTOR and p62 and decreased Beclin-1, LC3- II/I, and ULK1 in vitro. Our earlier research shows that RSM has defective autophagy. In the villi of RSM patients, there are fewer autophagosomes with an abnormal distribution. DSCs obtained from SM patients show insufficient autophagy with decreased Atg5, LC3B, and greater p62 levels [9, 10].

### Conclusion

In this article, we go through how autophagy controls important gestational processes such fertilization, embryonic development, trophoblast biochemistry, placental growth, decidualization, and the infiltration and habitation of decidual NK, macrophage, and T cells. There aren't many studies on autophagy in decidual macrophages and T cells, thus additional research is required. We also discuss relevant prospective therapeutic approaches for SM that target autophagy in light of the underlying processes of RM caused by abnormal autophagy. Rapamycin and vitamin D have garnered a lot of attention in recent years for their several functions in controlling trophoblast survival, decidualization, and immune milieu. What's more, autophagy is a dynamic mechanism that contributes to both preserving homeostasis and inflicting pathological harm when under stress.

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