Autophagy and cancer metastasis: a Trojan horse

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Metastasis is one of the most important challenges in cancer therapy strategies.[1] Therefore, understanding the mechanisms of metastasis is a powerful weapon to increase the survival of patients with cancer and improve their quality of life. For the first time, Jean Claude used the term 'metastasis' as one of the most important hallmarks of cancer in 1829.[2] Metastasis, a Greek word, means 'displacement' (meta meaning 'next' and stasis, 'placement').[3] This term refers to a general description of migration and invasion of tumor cells from the primary tumor site to secondary sites. Metastasis is considered as one of the key etiologies of cancer-related death; therefore, understanding its mechanism in depth has been always on demand in basic and clinical sciences.[4]

Epithelial to mesenchymal transition (EMT) is one of the several processes, which is involved in metastasis, and development of drug resistance in cancer.[5] During EMT, cells gradually convert from epithelial to a mesenchymal phenotype. This enables cancer cells to be more motile, have less extracellular matrix adhesion and be prone to detachment and moving toward distant organs. Beside metastasis, EMT is involved in embryonic development, wound healing, tissue fibrosis and scar formation.[6–8]

Macroautophagy (hereafter termed autophagy) is an essential physiologic pathway that is responsible for degradation of damaged organelles, misfolded proteins and pathogens.[9] The formation of double membrane vesicles (autophagosomes) to engulf the cytosolic material is the key step in autophagy pathway and is tightly regulated by autophagy-related genes (*ATG*).[10] Autophagosomes are fused to lysosomes for digestion via lysosomal degradation enzymes. Autophagy is a double-edged sword in tumor initiation and progression. Loss of autophagy machinery increases the rate of tumor initiation because of the accumulation of damaged mitochondria and accumulation of reactive oxygen species, leading to genomic damage and instability.[11] Interestingly, higher activation of autophagy in established tumors helps tumor cells to adapt to metabolic stress and lack of nutrients and support further tumor growth.[12 13]

There is a complex relation between EMT and autophagy in tumor cells. Several recent investigations have showed that inhibition of EMT in cancer cells induces autophagy, while inhibition of mTOR (autophagy induction) slows down the metastasis of cancer cells. For example, alteronol (protein kinase B (PKB, also known as Akt)/the mechanistic target of rapamycin (mTOR) inhibitor) induces autophagy in melanoma cancer cells and inhibits their metastasis and migration via inhibition of EMT.[14] On the other hand, our recent investigation showed that *ATG7* knock down and chemical inhibition of autophagy inhibit EMT and invasiveness of non-small cell lung cancer cells.[7 8] Alisertib (inhibitor of phosphatidylinositol 3-kinase (PI3K)/Akt/mTOR) induces autophagy and inhibits metastasis in ovarian cancers cells via inhibition of EMT.[15 16] Activation of PI3K/Akt/mTOR pathway induces EMT in several cancer models via activation of EMT transcription factors.[17] PI3K/Akt/mTOR pathway is also activated via different growth factors.[4] As an example, transforming growth factor beta (TGF-β) is one of the most important factors which activates EMT and is involved in the induction of the PI3K/Akt/mTOR pathway.[14 18 19] Inhibition of PI3K/Akt/mTOR pathway can be reversed using specific inhibitors of the pathway and decrease tumor metastasis.[15] On the other hand, TGF-β can induce simultaneous autophagy and EMT in several cancer models, while TGF-β-induced autophagy is necessary for its EMT induction.[7 8]

NF-κB is another factor that is involved in simultaneous regulation of EMT and autophagy.[14 20] It has been shown that it induces EMT and increases metastasis via activating EMT-related transcription factors (SNAIL, SLUG, SIP1, and TWIST).[20] On the other hand, NF-κB has a dual role in autophagy (inhibition and induction) by different mechanisms[14] which can negatively or positively regulate EMT and tumor invasion.

Besides NF-κB, p53 is also involved in the regulation of EMT and autophagy. It is a tumor-suppressing factor and plays a crucial role in the regulation of autophagy. Nuclear p53 induces autophagy via increasing the expression of *ATGs* and inhibition of PI3K/Akt/mTOR,[21–23] while cytosolic p53 inhibits autophagy via regulation of mTOR activation.[24 25] Under normal condition, p53 is localized in the cytoplasm and inhibits autophagy, while in the stress condition, p53 translocates to the nucleus and induces autophagy.[26] On the other hand, wild-type p53 inhibits EMT and metastasis via inhibition of transcription factors that are involved in the regulation of EMT.[27]

Overall, we can conclude that autophagy and EMT crosstalk is a complex mechanism (figure 1), is highly context dependent and can

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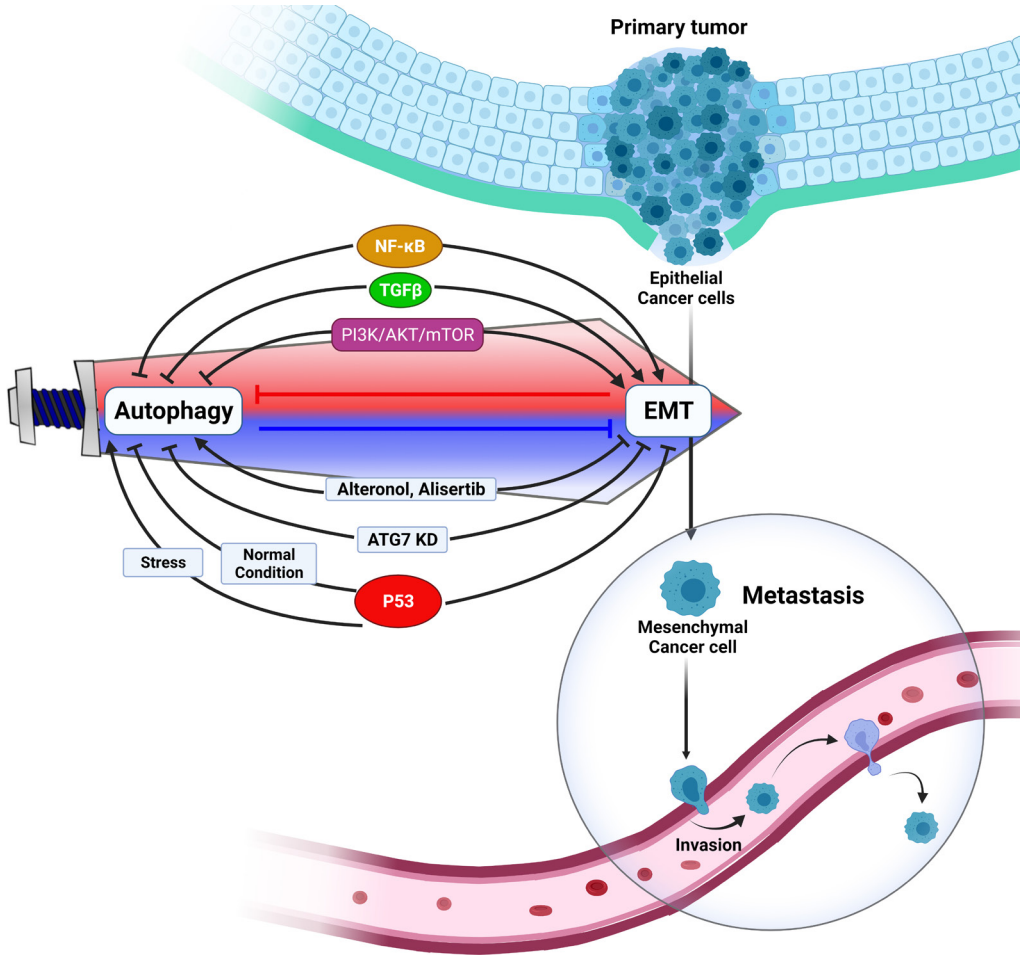

Figure 1 Complex crosstalk between autophagy and EMT during metastasis. Autophagy regulates cancer metastasis via EMT with different mechanisms. Several different regulators may target autophagy and indirectly affect EMT. These include p53 (cytosolic and nuclear), growth factors and cytokines (like TGF-β) and PI3K/AKT/mTOR pathway. Nuclear p53 increases autophagy, while cytosolic p53 inhibits this pathway. Regulation of autophagy pathway via Atg proteins (Atg7) also inhibits autophagy and decreases EMT and potentially inhibits cancer metastasis. Akt, protein kinase B; EMT, epithelial to mesenchymal transition; mTOR, the mechanistic target of rapamycin; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; PI3K, phosphatidylinositol 3-kinase; TGF-β, transforming growth factor beta.

be different in different types of cancers or different stages and grades of cancers. Therefore, it can be concluded that there is a complex crosstalk between autophagy and metastasis via regulation of EMT and targeting autophagy could be a potential mechanism to control cancer metastasis. In the meantime, extensive investigation on the regulation of metastasis via autophagy is needed to develop efficient inhibitors and inducers of autophagy to overcome cancer metastasis via autophagy pathway.

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