Understanding Role of NK Cells in Uterine Cancers

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Introduction

Cancer is one of the major health problem in the modern world. The incident of cancer is dependent on several factors, such as gender, genetics, immune status, and other environmental factors. Specifically, uterine cancers, which include endometrial cancer (EC) and cervical cancer (CC) are the most prevalent gynecologic malignancies amongst American women. About 83% of uterine cancer cases are endometrioid carcinomas, while fewer than 10% are sarcomas. Furthermore, the incidence of EC has continually increased over the past few decades. As of 2019, the rate of new uterine cancer cases is 28.4% with a 5.1% death rate and the 5-year relative survival from 2012 to 2018 is 81.3%.

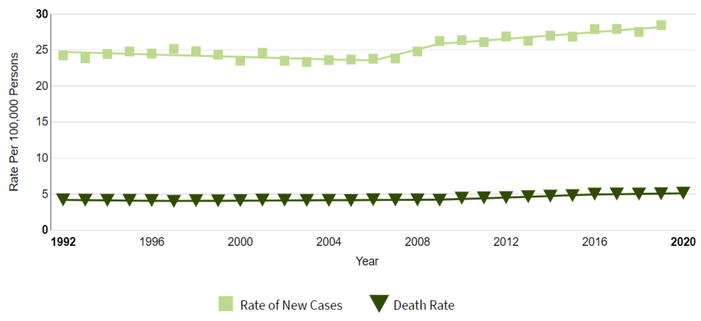


Figure 1. Incidence and mortality due to uterine cancer over past 30 years.

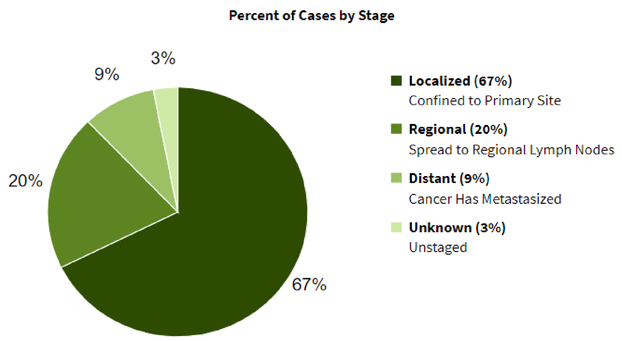


Figure 2. Different stages of uterine caner within 5-year relative survival.

NK cells are crucial immune cells in the female reproductive tract

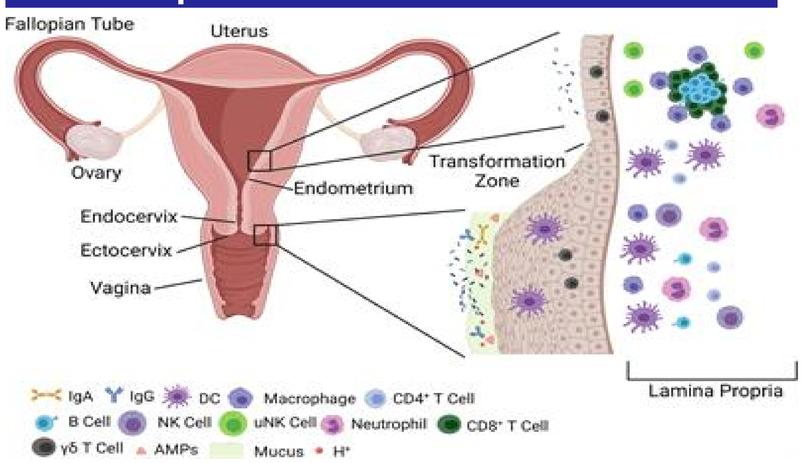
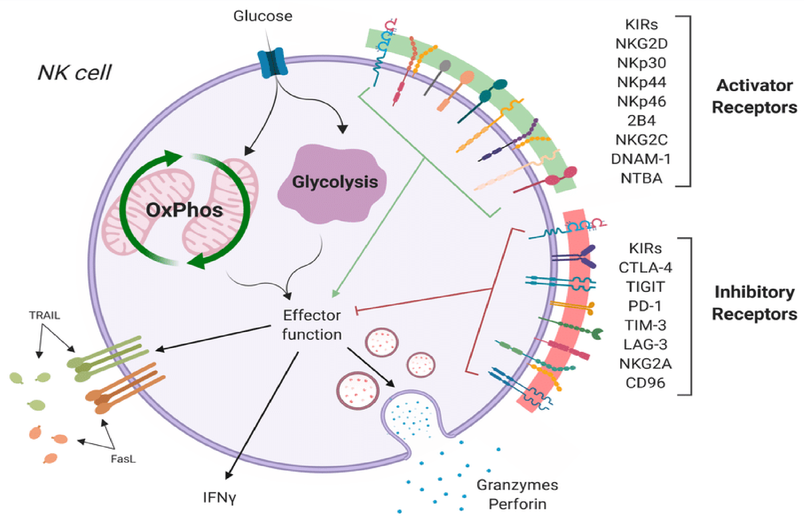


Figure 3. Immune environment in female reproductive tract.

NK cell in homeostasis



NK cells receptors and ligands in uterine cancer patients

The role of the immune system in cancer pathogenesis, including uterine cancer is well established. However, not much is known about the role of NK cells in uterine cancer pathogenesis, which is the focus of this paper. Nowadays NK cell-based immunotherapy are emerging, due to their cytotoxic actions on cancer cells. The table below shows the dysregulated NK cells governing their immune function in the uterine cancer tumor immune microenvironment (TIME).

Activating	Inhibitory
NKG2D ↓	KIR2DL1,2,3
NKG2C	KIR2DL5
FcγRIII	KIR3DL1
NKp30 ↓	LILRB1
NKp44	NKG2A ↑
NKp46 ↓	LAG-3
NKp80	KLRG1 ↑
DNAM-1 ↑	PD-1 ↑
2B4 (both of these are activating or inhibitory, depending on stage)	TIM-3
CRACC (CD2-like receptor-activating cytotoxic cell)	Siglec-3
CRTAM (Class I-restricted T cell-associated molecule)	Siglec-7
KIR2DS4	Siglect-9
KIR2DL4	TIGIT ↑
KIR3DS1	IAP
	NKRP1A
	LAIR-1
	IRp60
	Tactile
	IL1R8

NK cell in uterine cancer environment

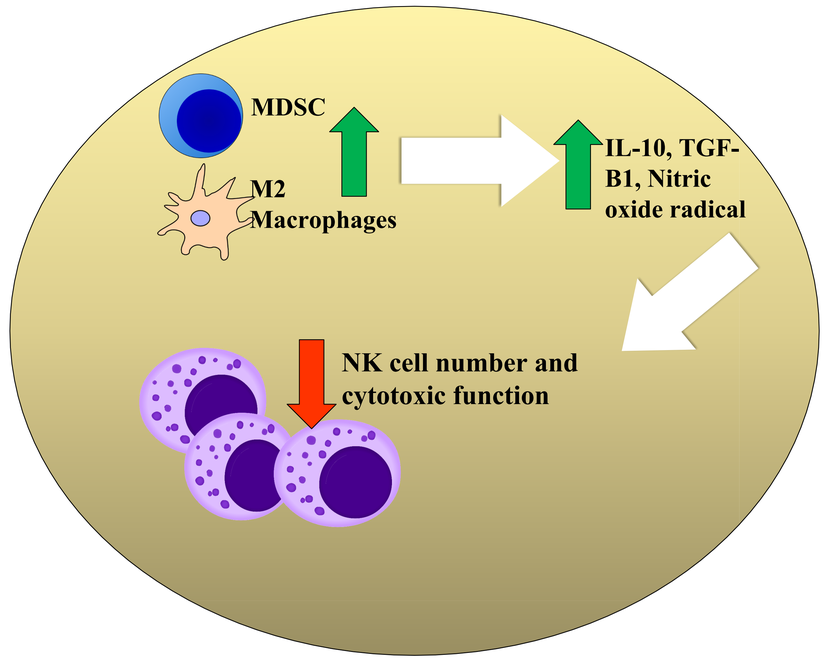


Figure 4. Impact of immunosuppressive environment on NK function and number. Increase in immunosuppressive cells (M2 macrophages and myeloid derived suppressor cell on uterine tumor causes the release of immunosuppressive molecules. This subsequently causes decrease in NK cell number and function downstream.

Future perspective and conclusion

Future uterine cancer treatment immunotherapy options ought to leverage the cytotoxic functions of NK cells to create more targeted cellular responses. For example, NK cell inhibitory receptors that are upregulated in uterine cancer such as NKG2A, KLRG1, PD-1, and TIGIT, can be helpful targets when devising an immunotherapeutic option for uterine cancer. Target based therapies, including NK cell based ones, may also increase the quality of life with less side effects. For example, allogenic NK cell therapy does not include the side effect of graft-versus host disease. Therefore, the development of novel NK cell targeted treatments are essential in creating more robust cures for uterine cancer.

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