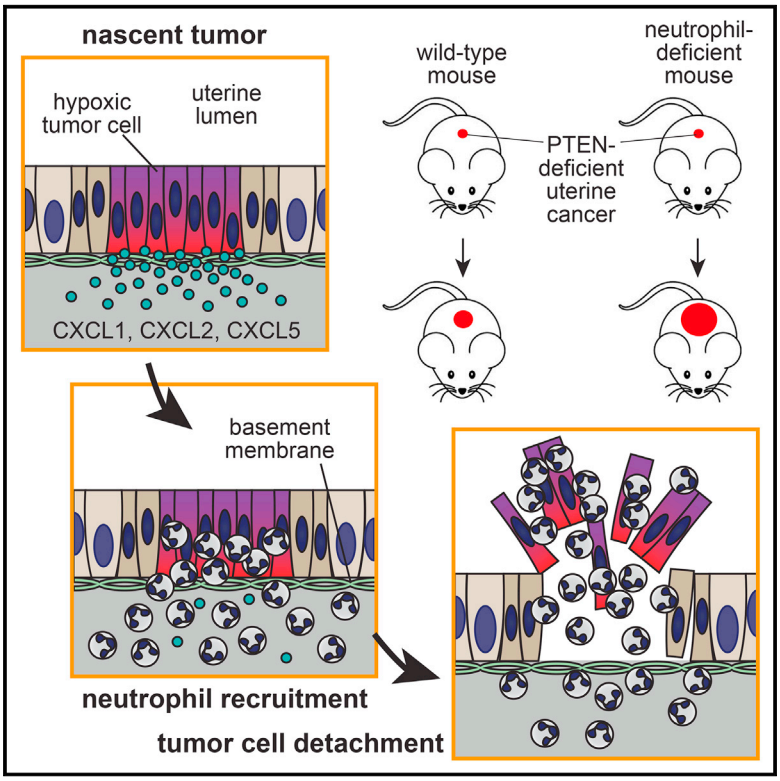
Article

Cancer Cell

Neutrophils Oppose Uterine Epithelial Carcinogenesis via Debridement of Hypoxic Tumor Cells

Graphical Abstract



Authors

Adam Blaisdell, Amandine Crequer, Devin Columbus, Takiko Daikoku, Khush Mittal, Sudhansu K. Dey, Adrian Erlebacher

Correspondence

adrian.erlebacher@nyumc.org

In Brief

Blaisdell et al. show in a mouse model of uterine cancer that polymorphonuclear neutrophil (PMN) recruitment resulting from tumor hypoxia impedes early tumor growth and malignant progression. A PMN gene signature correlates with improved survival in multiple human cancer types.

Highlights

- PMNs slow tumor growth and malignant progression in PTEN-deficient uterine tumors
- PMNs reduce tumor burden by promoting tumor cell basement membrane detachment
- Anti-tumor PMN activity does not require other leukocytes or tumor cell senescence
- PMN recruitment to early-stage tumors is linked to hypoxia-induced inflammation

Accession Numbers

GSE73541

Blaisdell et al., 2015, Cancer Cell *28*, 785–799
December 14, 2015
http://dx.doi.org/10.1016/j.ccell.2015.11.005

Cancer Cell
Article

Neutrophils Oppose Uterine Epithelial Carcinogenesis via Debridement of Hypoxic Tumor Cells

Adam Blaisdell,[1] Amandine Crequer,[1] Devin Columbus,[1] Takiko Daikoku,[2,4] Khush Mittal,[1] Sudhansu K. Dey,[2] and Adrian Erlebacher[1,3,*]
[1]Department of Pathology, NYU School of Medicine, New York, NY 10016, USA
[2]Division of Reproductive Sciences, Cincinnati Children's Hospital Medical Center, Cincinnati, OH 45229, USA
[3]NYU Cancer Institute, NYU Langone Medical Center, New York, NY 10016, USA
[4]Present address: Division of Transgenic Animal Science, Advanced Science Research Center, Kanazawa University, Kanazawa 920-1192, Japan
*Correspondence: adrian.erlebacher@nyumc.org
http://dx.doi.org/10.1016/j.ccell.2015.11.005

SUMMARY

Polymorphonuclear neutrophils (PMNs) are largely considered to foster cancer development despite wielding an arsenal of cytotoxic agents. Using a mouse model of PTEN-deficient uterine cancer, we describe a surprising inhibitory role for PMNs in epithelial carcinogenesis. By inducing tumor cell detachment from the basement membrane, PMNs impeded early-stage tumor growth and retarded malignant progression. Unexpectedly, PMN recruitment and tumor growth control occurred independently of lymphocytes and cellular senescence and instead ensued as part of the tumor's intrinsic inflammatory response to hypoxia. In humans, a PMN gene signature correlated with improved survival in several cancer subtypes, including PTEN-deficient uterine cancer. These findings provide insight into tumor-associated PMNs and reveal a context-specific capacity for PMNs to directly combat tumorigenesis.

INTRODUCTION

Inflammation pervades virtually all forms of cancer even from the earliest stages of tumor development. Danger signals emanating from the tumor elicit local production of inflammatory cytokines and chemokines that subsequently draw inflammatory leukocytes into the neoplastic tissue. In general, inflammation is thought to nourish tumor growth and accelerate malignant progression (Trinchieri, 2012). However, certain inflammatory effectors within the tumor microenvironment remain functionally anti-tumor, particularly those that either block tumor cell proliferation or induce tumor cell death. Harnessing the power of these effectors represents a significant therapeutic challenge and requires a better understanding of the pathways that govern tumor-associated inflammation.

Polymorphonuclear neutrophils (PMNs) rapidly and ubiquitously infiltrate inflamed tissue and thus likely dominate even the earliest interactions of the host immune system with a nascent tumor. In line with the literature on tumor-associated inflammation, the vast majority of recent work on PMNs in cancer has ascribed to them pro-tumorigenic properties (Brandau et al., 2013). Tumor-associated PMNs have variously been shown to stimulate tumor cell proliferation, block cellular senescence, promote angiogenesis, and inhibit the tumor-associated adaptive immune response. On the other hand, activated PMNs robustly produce a variety of toxic compounds and can induce tumor cell cytolysis or cytostasis in vitro, which suggests that in certain circumstances they might oppose tumorigenesis (reviewed in Souto et al., 2011). Indeed, PMNs can inhibit growth of tumors engineered to recruit them in high numbers and have long been thought to be critical in vivo effectors of antibody-mediated tumor cell lysis (Albanesi et al., 2013; Souto et al., 2011). More recently, PMNs have been suggested to unleash the anti-tumor potential of cytotoxic T cells (Fridlender et al., 2009; Kousis et al., 2007) and to oppose seeding of metastatic tumor cells at distal tissue sites (Granot et al., 2011). Critically, all of this work employed transplantable tumor models, which thus leaves unaddressed the capacity of PMNs to combat primary, autochthonous tumorigenesis. Additionally, whether PMNs can resist cancer development independently of other immune cells or therapeutic manipulation remains unknown. These questions are particularly relevant to the early stages of tumorigenesis,

Significance

We present evidence in mice and humans that PMNs provide an endogenous defense mechanism against cancer of the uterus. Our work also unexpectedly suggests that PMNs are recruited to the tumor-bearing mouse uterus as a result of tumor hypoxia rather than anti-tumor adaptive immunity or tumor cell senescence. These results reveal an innate immune cell-mediated pathway of cancer resistance and support efforts to harness PMNs therapeutically to combat cancer.