

Supercharging the immune system to destroy tumors

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The Paust Laboratory at Scripps Research

Silke's journey to being an immunologist:

10th grade: Decided to become an immunologist upon learning about the immune system in high school BS, Biochemistry, University of Wisconsin – Madison PhD, Immunology, Harvard University, Boston, MA

As a postdoctoral fellow, I started to work on "Natural Killer" cells supported by the Irvington Fellowship of the Cancer Research Institute, the Ragon Fellowship at Harvard, MIT, and MGH, and the NIH T32 Key findings: Natural Killer cells remember prior pathogens encounters and are long-lived immune cells.

2013-2018 Assistant Professor - Baylor College of Medicine, Houston, TX 2018 Paust lab moves to Scripps Research We seek to understand how Natural Killer cells can be used clinically to prevent or treat human disease.



Paust Lab 2018



Scripps Research 2019



Paust Lab 2022



Overview

- The human pancreas and pancreatic cancer facts
- Immune cells protect us from cancer
- Failure of immunotherapy to cure pancreatic cancer
- Learning from the immunological landscape of pancreatic cancer
- Supercharging Natural Born Killers to cure pancreatic cancer
- Summary and outlook



Natural Killer cell with lytic granules (in red) Courtesy of Dr. Emily Mace (Columbia U)



Anatomy and function of the pancreas

The pancreas helps digestion and regulates blood sugar.

- The exocrine portion secretes digestive enzymes that help digest dietary fat and protein.
- The endocrine portion secretes its hormones into the blood stream, including insulin and glucagon to regulate blood sugar.





Pancreatic cancer

- About 60,000 pancreatic cancer diagnoses and 50,000 deaths annually in the US
- Pancreatic cancer has the highest mortality rate of all cancers
- Pancreatic cancer is the 3rd leading cause of cancer-related death (after lung and colon cancer)
- The overall 5-year survival rate is ~ 9%
- 95% of pancreatic cancer is pancreatic duct adenocarcinoma (PDAC)
- 5% of pancreatic cancer are neuroendocrine or islet cell tumors



American Cancer Society, Cancer Facts and Figures, 2020; Cancer.org



Pancreatic cancer survival rates have not improved in the past 50 years





Pancreatic cancer is often caught too late – after it has spread to other organs



Pancreatic cancer metastasizes to the stomach, liver, lung, and other sites



Conventional therapies are the only FDA approved option – with low response rates



Panchal, International Immunopharmacology, 2021



Immune cells protect us from cancer

T cells require prior activation and recognize specific tumor antigens. Once activated, T cells will kill tumor cells expressing those tumor antigens.



Adapted from "T Cell Activation in Cancer" by BioRender.com (2021). Retrieved from https://app.biorender.com/biorender-templates.



Examples of tumor-fighting immune cells

T cells require prior activation and recognize specific tumor antigens. Once activated, T cells will kill tumor cells expressing those tumor antigens.



Natural Killer cells are "Natural Born Killers" and kill stressed cells without needing prior activation.



Adapted from "T Cell Activation in Cancer" by BioRender.com (2021). Retrieved from https://app.biorender.com/biorender-templates.



Annual Rev. Imunol.2005.23:225-74

Over time, tumor-fighting Natural Killer cells exhaust





Tumors ligate "off switches" on exhausted Natural Killer cells





Immune checkpoint inhibition therapy blocks off-switches to improve the anti-tumor immune response

- Within the past 20 years, drugs have been developed to block immune checkpoints.
- Immune checkpoint inhibition
 - is often better tolerated than chemotherapy
 - is potentially a "cure" even in metastatic disease, albeit only a proportion of patients benefit
 - is used in a variety of solid and hematologic malignancies
 - biomarkers are available to predict the response to therapy
- Immune checkpoint inhibition is thought to re-activate exhausted T cells to fight tumors



Checkpoint blockade improves Lung Cancer patient survival



Avelumab = PD-1 blockade Docetaxel = chemotherapy



Lung Cancer 2021 15492-98DOI: (10.1016/j.lungcan.2021.01.026)





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Summary I

- Within the past 40 years, overall survival has not significantly improved for persons with pancreatic cancer
- Immune cells fight cancer but get tired when exposed to tumors for long periods of time
- Some of the causes of immune cell exhaustion are known and can be targeted with FDA-approved drugs
- These drugs work for several liquid and solid tumors, but not for pancreatic cancer
- As pancreatic cancer is unresponsive to immune checkpoint inhibition, new therapeutic approaches are needed

What other components of the immune system can we harness to eradicate pancreatic cancer?



Pancreatic tumors are fortresses preventing immune cell infiltration



Ho, Nature Reviews Clinical Oncology volume 17, pages527–540 (2020)



Pancreatic tumors are mostly devoid of immune cells

Pancreatic cancer

Lung Cancer



Zalfa, et. al., in peer review



Twenty percent of pancreatic tumor's immune cells are Natural Killer cells

Pancreatic Cancer



- 20% of PDACs NK cells are immune cells
- NK cells outnumber CTLs in PDAC

Zalfa, et. al., in peer review



Natural Killer cells infiltrate the tumor while T cells get stuck in the stroma



N= 16 treatment naïve PDAC donors





- NK cells are equally distributed in tumor and stroma
- CTLs are elevated in the stroma and lacking in the tumor
- Higher numbers of NK cells are closer to the tumor than CTLs







THE FRONT ROW

at Scripps Research

cells

Killing

Pancreatic cancer cells express stress ligan but intra-tumoral Natural Ki









Zalfa, et. al., in peer review

Summary II

- Natural Killer cells infiltrate pancreatic cancer despite its hostile fibrous stroma
- In contrast to Natural Killer cells, tumor-fighting T cells get stuck in the tumor stroma
- This may explain why prior Immunotherapy didn't work (T cells could not infiltrate the tumor)
- Pancreatic cancer cells express stress ligands that activate Natural Killer cells
- Natural Killer cells are exhausted in pancreatic tumors, thus tumors grow despite their stress ligand expression

Can we use activated Natural Killer cells as immunotherapy infusions to kill pancreatic cancer cells?

Supercharging Natural Killer cells to kill pancreatic cancer

Peripheral blood Natural Killer cells (healthy donor)

Activating receptor responsive to tumor expressed stress ligands

Supercharged Natural Killer cells kill pancreatic cancer cells in vitro

When co-incubated with activated NK cells, 20 – 80% of tumor cells are killed within six hours

Putting human pancreatic cancer tissue pieces into mice with no immune system allows a tumor to grow and the testing of immuno-therapies

Surgical implantation of human PDAC into the tail of the mouse's pancreas

Monitor tumor growth

by ultrasound

Immune deficient mouse

Natural Killer cell immunotherapy eradicates human pancreatic cancer in most treated animals

Immune deficient mouse growing a human pancreatic tumor

- Mice were infused with NK cell therapy once human pancreatic tumors reached 7 mm³ (the equivalent of a 1.3-inch cubed tumor in humans)
- Activated Natural Killer cells eliminate pancreatic cancer in mice with human pancreatic tumors
- One-half of mice in complete remission remain tumorfree for at least 6 months after therapy was stopped

Conclusion

- Due to the tumor's hostile stroma, immune cell infiltration is low in pancreatic cancer
- Nevertheless, 20% of intratumoral immune cells are Natural Killer cells
- More Natural Killer cells are located closer to tumor cells than tumor-fighting T cells
- Tumor-fighting T cells get stuck in the tumor stroma and do not reach the tumor cells
- In growing tumors, Natural Killer cells are tired, and do not kill the tumor
- Healthy, activated Natural Killer cells kill pancreatic cancer cells in vitro
- Healthy, activated Natural Killer cells eliminate pancreatic cancer in mice with human pancreatic tumors
- One half of mice cured from human pancreatic cancer remain tumor and metastasis free for at least six months post therapy

Future Directions

- To improve the Natural Killer cell infusion product to lower the required number of infusions
- To identify the mechanisms Natural Killer cells use to exit the tumor stroma to migrate into the tumor
- To engineer tumor-fighting T cells to migrate close to the tumor for tumor cell killing
- To determine the effects of Natural Killer cell therapy on the tumor's metastatic potential
- To publish our results to encourage the evaluation of this therapy in clinical trials

> To significantly increase pancreatic cancer survival and cure rates!

Science is Teamwork – Thank you, Team!

Dr. Cristina Zalfa Post-doc (Scripps Research)

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<u>FUNDING:</u> Scripps Research, La Jolla, CA

Persons donating tumor tissue to research!

<u>Collaborators:</u> Dr. Becke White (UCSD) Dr. Jayanth Shankara Narayanan (UCSD) Dr. Mojgan Hosseini (UCSD) Dr. Dan Kaufman (UCSD) Dr. Zbigniew Mikulski (LJI)

The UCSD Biorepository at the Moores Cancer Center at UCSD

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