Synopsis:

- Chronic inflammation, a hallmark of solid tumor, is strongly associated with poor disease outcome in patients with breast cancer[1]. In addition, heterogeniety of breast cancer poses a major clinical challenge in diagnosis and treatment of both primary and metastatic forms[2]. The specific role of chronic inflammation in promoting heterogenous structure and metastatic progression of breast cancer is not well understood[3].

- Selective amplification or loss of genes involved in regulation of inflammatory pathways represents an adaptive evolutionary mechanism to evade immune recognition and promote survival of the malignant cells in the heterogenous tumor microenvironment (TME)[4, 5]. This also constitute an important mechanism in tumor progression from primary neoplasms to metastatic tumors.

- Immuno-metabolic crosstalk regulated by both cell-intrinsic inflammatory pathways and its immune microenvironment, is a strong driver of tumor heterogeneity observed in breast cancer[6, 7]. Cancer cell-intrinsic control of inflammatory pathways by innate immune regulators plays a key protumoral role by altering the levels of proinflammatory cytokines in TME. For example, An increased level of TNF-α in TME regulates immune response and survival of breast cancer cells[8].

- The differential expression of these innate immune regulators in primary and metastatic-breast cancer cells controls the outcome of innate immune signaling from lethal to a survival mechanism in an inflammatory microenvironment[9]. Hence, modulation of immune responses via immunothreapies has raised hopes for an effective therapeutic strategy for breast cancer[10]. However, only a subset of patients benefit from targeted-immunnotherapy, highlighting the need for a better understanding of tumor-immune crosstalk and improvement of current treatment modalities.

- Mitochondria are the central participant in regulating the metabolic adaptation and chronic inflammatory response during tumor growth and development[7]. Emerging evidences suggest the role of mitochondria-localized immune adaptor proteins including MAVS and STING in sensing stress has been co-opted as an indirect mechanism to regulate the inflammatory response and metabolic adaption resulting from intrinsic cellular damage[11]. NLRX1, a mitochondria-localized NOD-like receptor (NLR) family protein, regulates innate immune signaling and mitochondrial metabolism in different models of cancer and infection[12-15].

- Given the role of mitochondria as an intracellular signalling platform, we would discuss the role of both MAVS and NLRX1 as potential regulators of immunometabolic functions which may integrate innate immune responses and mitochondrial function to regulate the tumorigenic potential of cancer cells. NLRX1 expression in different breast cancer types would significantly influence tumor progression and metastasis. We would further highlight the dynamic regulation of mitochondrial function by innate immune signaling proteins to adapt cellular metabolism and support survival and proliferation of cancer cells.

References:

1. Diakos, C.I. et al. (2014) Cancer-related inflammation and treatment effectiveness. Lancet Oncol 15 (11), e493-503.
2. Marusyk, A. et al. (2014) Non-cell-autonomous driving of tumour growth supports sub-clonal heterogeneity. Nature 514 (7520), 54-8.
3. Bianchini, G. et al. (2016) Triple-negative breast cancer: challenges and opportunities of a heterogeneous disease. Nat Rev Clin Oncol 13 (11), 674-690.
4. Wellenstein, M.D. and de Visser, K.E. (2018) Cancer-Cell-Intrinsic Mechanisms Shaping the Tumor Immune Landscape. Immunity 48 (3), 399-416.
5. Wellenstein, M.D. et al. (2019) Loss of p53 triggers WNT-dependent systemic inflammation to drive breast cancer metastasis. Nature 572 (7770), 538-542.
6. Gruosso, T. et al. (2019) Spatially distinct tumor immune microenvironments stratify triple-negative breast cancers. J Clin Invest 129 (4), 1785-1800.
7. Lyssiotis, C.A. and Kimmelman, A.C. (2017) Metabolic Interactions in the Tumor Microenvironment. Trends Cell Biol 27 (11), 863-875.
8. Lippitz, B.E. (2013) Cytokine patterns in patients with cancer: a systematic review. Lancet Oncol 14 (6), e218-28.
9. Bakhoum, S.F. et al. (2018) Chromosomal instability drives metastasis through a cytosolic DNA response. Nature 553 (7689), 467-472.

10. Solinas, C. et al. (2017) Targeting immune checkpoints in breast cancer: an update of early results. ESMO Open 2 (5), e000255.
11. Weinberg, S.E. et al. (2015) Mitochondria in the regulation of innate and adaptive immunity. Immunity 42 (3), 406-17.
12. Leber, A. et al. (2017) NLRX1 Regulates Effector and Metabolic Functions of CD4(+) T Cells. J Immunol 198 (6), 2260-2268.
13. Singh, K. et al. (2015) NLRX1 acts as tumor suppressor by regulating TNF-alpha induced apoptosis and metabolism in cancer cells. Biochim Biophys Acta 1853 (5), 1073-86.
14. Singh, K. et al. (2019) NLRX1 regulates TNF-alpha-induced mitochondria-lysosomal crosstalk to maintain the invasive and metastatic potential of breast cancer cells. Biochim Biophys Acta Mol Basis Dis 1865 (6), 1460-1476.
15. Zhang, Y. et al. (2019) Listeria hijacks host mitophagy through a novel mitophagy receptor to evade killing. Nat Immunol 20 (4), 433-446.