Congratulations to IMCB's latest PhD graduate – Max KOSOK

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Thesis Title: Dissecting Breast Cancer Heterogeneity by Advanced Proteomics Mass Spectrometry for Idenifying Subclass-Specific Therapeutics

Breast cancer, the most common cancer in women worldwide, is a highly heterogeneous disease responsible for the highest mortality in female cancer patients. Currently, breast cancer is subcategorized into three subtypes based on expression of particular receptors for patient stratification towards suitable clinical intervention. These include two receptor-positive subtypes, estrogen/progesterone receptor positive (ER+/PR+) and human epidermal growth factor receptor 2 positive (HER2+), and a receptor negative subtype, triple-negative breast cancer (TNBC), that does not express any of the three receptors. While targeted therapies exist for receptor positive subtypes, TNBC lacks effective treatment and currently relies on pre- and post-operative chemotherapy. High intrinsic heterogeneity and lack of clear oncogenic drivers impedes precise understanding of dysregulated mechanisms and consequentially hinders development of better targeted breast cancer therapies. Systematic dissection of breast cancer heterogeneity is therefore required to extract dysregulated

pathways and associated potential therapeutic targets pertaining to each subtype and beyond. With the hypothesis that breast cancer, in particular TNBC, has distinct subclasses based on protein expression profiles, comprehensive unbiased protein profiling of breast cancer cells was performed in this study. Using strategized mass spectrometry-based proteomics and advanced computational analysis, three breast cancer subclasses, luminal, basal A and basal B, with distinct proteomic profiles and associated molecular mechanisms were identified. The analyses revealed that kinases and proteases displayed unique expression patterns within these subclasses, indicating prominent roles in orchestrating discrete molecular functions in a subclass-specific manner. Protein interaction network analysis as well as protein co-regulation analysis with emphasis on these two protein classes unravelled dysregulated biological processes, pathways, and possible targets for each subclass. Cancer hallmarks including estrogen response and fatty acid metabolism were preferentially enriched in the luminal subclass, while the basal A subclass displayed functional bias towards interferon signalling. The basal B subclass was associated with aggressive cancer processes including EMT, hypoxia and PI3K-AKT signalling. Of note, kinase AXL and protease FAP were identified as oncogenic drivers mediating invasion, metastasis and EMT, specifically within the aggressive basal B subclass. Validation experiments confirmed subclass-specific roles of AXL and FAP in driving invasion, hence highlighting distinct involvement of proteases and kinases in subclass-specific regulations of tumorigenesis within TNBC. In all, this study uncovered subtype-specific dysregulations in breast cancer, particularly TNBC subclass-specific therapeutic targets, which opens new avenues for rigorous validation to explore their clinical utility for personalized breast cancer treatment.

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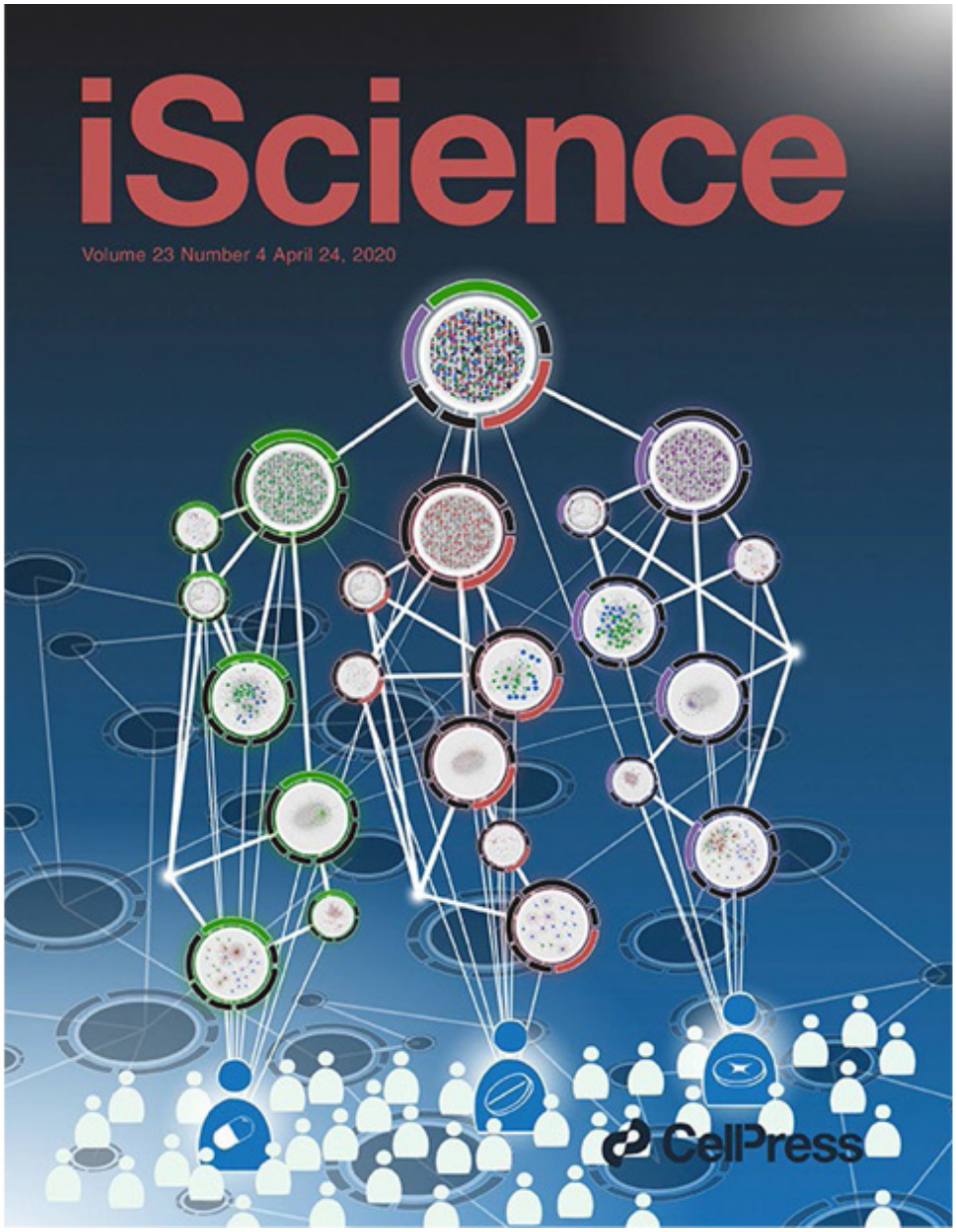

On the Cover: The image symbolizes the intrinsic heterogeneity of cancer and emphasizes the need for dissecting subclass-specific mechanisms for tailoring personalized targeted therapies. Integrating mass-spectrometry-based proteomics with computational analysis, the work by Kosok, Alli-Shaik, et al. unveiled subclass-specific functional associations, pathway aberrations, and molecular vulnerabilities within different breast cancer subtypes, more specifically within the highly aggressive triple-negative breast cancer (TNBC). Rationalizing therapies based on such dysregulated pathways and perturbed molecular targets, coupled with patient stratification, holds great potential for precision medicine in breast cancer. Artwork by Max Kosok. See Kosok et al., vol. 23, 2020. https://www.cell.com/iscience/fulltext/S2589-0042(20)30051-1