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Activation of FcγR-dependent responses to therapeutic antibodies by nurse like cells requires PI3Kδ

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Antibody therapies for treating chronic lymphocytic leukemia (CLL) remain a challenge for many CLL patients who are insensitive to antibody treatment. A high percentage of CLL patients that are resistant to the current combination therapy of chemotherapeutics and immune-therapeutics have always been a clinical challenge. Understanding the mechanisms driving disease progression and treatment resistance is key to improving patient outcomes. Many studies including our own laboratories have shown that resistance to therapeutic antibodies against CLL is due to the survival signals from the monocyte derived macrophages (MDMs) and also an acquired resistance of monocyte derived macrophages to participate in FcγR-dependent anti-tumor responses. However, the FcγR-dependent signaling pathway in macrophages has not been well studied. Our recently published data suggested that SYK and BTK are involved downstream of FcγR-dependent signaling pathway. In this study we investigate the involvement of PI3K isoforms as they have been known to be an important pathway regulator for cellular function in various immune cells such as T cells, B cells and NK cells as well as in cancerous cells. To examine the expression and involvement PI3K isoforms in contributing to FcγR-dependent ADCC by MDMs, we used different inhibitors to specifically target each PI3K isoform at a time to investigate the effect on ADCC responses by MDMs. Examination of PI3K expression showed that PI3Kα, β and δ are expressed in MDM whereas PI3Kγ is below the limit of detection. We also reported that the PI3Kδ-selective inhibitor, idelalisib and the pan PI3K inhibitor BKM120 (Buparlisib) were able to inhibit ADCC in response to the CD20-targeting therapeutic antibody, obinutuzumab. Similarly, both buparlisib and idelalisib were able to inhibit AKT phosphorylation at concentrations that also inhibited ADCC. This is the first report to show that PI3Kδ is involved in FcγR signaling in MDMs from CLL patients or in MDMs from any tumor type. Based on these findings we conclude that PI3Kδ is a critical effector molecule for anti-tumor responses to therapeutic antibodies in CLL.

Biography

Yu-Chen Enya Chen is pursuing her PhD degree at University of Queensland. She has published a review paper as first author in BBA Cancer Review 2017 (*Chen et al.*). Her PhD project so far has presented an interesting study towards the understanding of the antibody resistant of patients with progressive chronic lymphocytic leukemia disease.

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