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Titolo	THE ROLE OF CHI3L1 IN BREAST CANCER¿A DRIVER OF IMMUNOSUPPRESSION ON THE ROADOF TUMOR PROGRESSION¿ [Tesi di dottorato]
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Sommario	The human epidermal growth factor receptor-2 (HER2) is one of the most valuable targets in cancer. HER2 is responsible for the pathogenesis of 20% of breast carcinomas (BC) and is associated with an aggressive phenotype. Despite the remarkable improvement in survival obtained by the anti-HER2 monoclonal antibodies, Trastuzumab and Pertuzumab, half of the patients still progress in less than two years. Because Antibody-dependent cytotoxicity (ADCC) mediated by NK cells is a major determinant of these antibodies' efficacy, we wanted to assess whether the development of resistance is associated with a decreased NK cell activity and to identify molecular mediators of resistance. We analyzed the sera from a cohort of HER2+ BC patients undergoing Trastuzumab treatment and showed that NK cells treated with non-responders’ sera have impaired ADCC. We identified Chitinase 3 like-1 protein (CHI3L1/YKL-40) as a potential mediator of resistance as its levels were elevated in sera of resistant patients compared to complete remission patients and healthy controls. We found that CHI3L1 inhibits healthy NK cell and CD8 T cell cytotoxicity by interfering with the polarization of the microtubule-organizing center (MTOC) and lytic granules to the immune synapse. CHI3L1

	mediates its effect by modulating the receptor of advanced glycation end products (RAGE) and its downstream JNK signaling leading to paralysis of the NK lytic machinery. In vivo, injecting mice with CHI3L1 drastically increased the growth of RMA-S (NK sensitive) tumors. Similarly, CHI3L1 overexpression enhanced the growth of HER2+ BC Xenografts and abrogated the control of tumor growth by ADCC in Trastuzumab treated mice. Finally, a CHI3L1 neutralizing antibody in combination with Trastuzumab was able to cure mice with HER2 xenografts by restoring NK cell activity. Our work identifies CHI3L1 as an important mediator of resistance to HER2 targeted therapy and a potential soluble immune checkpoint of NK cells and CD8 T cells beyond Trastuzumab and Breast cancer.
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