c-Myc dependent expression of pro-apoptotic Bim renders HER2-overexpressing breast cancer cells dependent on anti-apoptotic Mcl-1

Submitted by Emmanuel Lemoine on Thu, 03/26/2015 - 14:22

Titre c-Myc dependent expression of pro-apoptotic Bim renders HER2-overexpressing breast cancer cells dependent on anti-apoptotic Mcl-1

Type de publication Article de revue

Auteur Campone, Mario [1], Noël, Bélinda [2], Couriaud, Cécile [3], Grau, Morgan [4], Guillemin, Yannis [5], Gautier, Fabien [6], Gouraud, Wilfried [7], Charbonnel, Catherine [8], Campion, Loïc [9], Jézéquel, Pascal [10], Braun, Frédérique [11], Barré, Benjamin [12], Coqueret, Olivier [13], Barillé-Nion, Sophie [14], Juin, Philippe [15]

Type Article scientifique dans une revue à comité de lecture

Année 2011

Langue Anglais

Date 2011/09/07

Numéro 1

Pagination 1 - 14

Volume 10

Titre de la revue Molecular Cancer

ISSN 1476-4598

Mots-clés Cancer Research [16], Oncology [17]
Background Anti-apoptotic signals induced downstream of HER2 are known to contribute to the resistance to current treatments of breast cancer cells that overexpress this member of the EGFR family. Whether or not some of these signals are also involved in tumor maintenance by counteracting constitutive death signals is much less understood. To address this, we investigated what role anti- and pro-apoptotic Bcl-2 family members, key regulators of cancer cell survival, might play in the viability of HER2 overexpressing breast cancer cells. Methods We used cell lines as an in vitro model of HER2-overexpressing cells in order to evaluate how anti-apoptotic Bcl-2, Bcl-xL and Mcl-1, and pro-apoptotic Puma and Bim impact on their survival, and to investigate how the constitutive expression of these proteins is regulated. Expression of the proteins of interest was confirmed using lysates from HER2-overexpressing tumors and through analysis of publicly available RNA expression data. Results We show that the depletion of Mcl-1 is sufficient to induce apoptosis in HER2-overexpressing breast cancer cells. This Mcl-1 dependence is due to Bim expression and it directly results from oncogenic signaling, as depletion of the oncoprotein c-Myc, which occupies regions of the Bim promoter as evaluated in ChIP assays, decreases Bim levels and mitigates Mcl-1 dependence. Consistently, a reduction of c-Myc expression by inhibition of mTORC1 activity abrogates occupancy of the Bim promoter by c-Myc, decreases Bim expression and promotes tolerance to Mcl-1 depletion. Western blot analysis confirms that naïve HER2-overexpressing tumors constitutively express detectable levels of Mcl-1 and Bim, while expression data hint on enrichment for Mcl-1 transcripts in these tumors. Conclusions This work establishes that, in HER2-overexpressing tumors, it is necessary, and maybe sufficient, to therapeutically impact on the Mcl-1/Bim balance for efficient induction of cancer cell death.
[19] http://dx.doi.org/10.1186/1476-4598-10-110

Publié sur Okina (http://okina.univ-angers.fr)