Potential relationship between the expression of Cx26/Cx43 and the BRAF mutation status in human melanoma cells

1)Polini B. 2)Matii L. 3)Moscato S. 4)Carpi S. 5)Breschi MC. 6)Nieri P. 7)Fogli S.

Universuty of Pisa

Cutaneous melanoma is the most aggressive skin cancer with a 5-year survival rate critically depending on disease stage (American Cancer Society, 2016). Notwithstanding new drugs have recently been developed for advanced melanoma treatment, the better understanding of the mechanisms involved in metastasis development are pivotal to design novel pharmacological strategies aimed at improving survival. Connexins (Cx) are a class of proteins reported to be implicated in the development and progression of different types of tumors, including cutaneous melanoma. Indeed, they are implicated in cellular homeostasis via intercellular, extracellular and intracellular communication signaling (Vinken et al., 2006). Although Cx have been classified as conditional tumor suppressors, that is proteins playing different roles depending on the stage and type of the tumor (Ableser et al., 2014), their role in the neoplastic phenotype of human melanoma cells remains controversial and unclear.

The present study was aimed at elucidating the functional significance of Cx26 and Cx43 in human melanoma cell lines derived from tumors with different origin (primitive or metastatic) and genotype (BRAF mutated or wild type). Particularly, we analyzed their gene expression by Real-Time PCR and sub-cellular location by immunocytochemistry. Cx26 and Cx43 gene expression appeared to be related with BRAF mutation status since it linearly increased in wild-type melanoma cells as compared to those having BRAF heterozygous or homozygous variants. According to this notion, the selective BRAF inhibitor vemurafenib at 10 μM, significantly decreased Cx26 and Cx43 gene expression in BRAF mutant cells and such an effect was confirmed by immunohistochemistry. Our findings also showed different sub-cellular localization in the melanoma cell lines tested. Specifically, Cx26 was mostly localized in the nucleus and the cytoplasm in MeWo cells, the plasma membrane in 501-Mel cells and the cytoplasm in A375 cells. At variance with this, Cx43 was predominantly localized in the cytoplasm in MeWo and 501-Mel cells and in the plasma membrane in A375 cells. Overall, our findings support a possible functional relationship between the expression of Cx26/Cx43 and the BRAF mutation status in human melanoma cells, thus improving our understanding of the complex role of Cx in human melanoma.

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Vinken et al., Cellular Signalling, 2006. 18: p. 592–600.

Ableser et al., The Journal of Biological Chemistry, 2014. 289: p. 1592–1603.