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Hypoxia induces phenotypic plasticity in melanoma via the novel tyrosine kinase receptors ROR1 and ROR2

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Abstract

Phenotypic plasticity in melanoma is marked by an increase in Wnt5A signaling. We have defined the role of the Wnt5A co-receptors ROR1 and ROR2, not previously associated with melanoma, and interrogated their roles in phenotype switching. We have demonstrated that ROR1 is associated with a more proliferative, non-metastatic, melanocytic phenotype, whereas ROR2 is associated with a less proliferative, invasive, mesenchymal phenotype. Expression of these receptors appears to be almost mutually exclusive, as the expression of ROR2 can downregulate that of ROR1. The change from a melanocytic, ROR1 high phenotype to a mesenchymal, ROR2 high one can be induced by a hypoxic microenvironment. Importantly, we show that the Wnt5A/ROR2 signaling pathway is critical for the stabilization of Hif1a via SIAH2. In BRAF mutant cells, this phenotypic switch to a non-canonical Wnt signaling pathway predicts an increased resistance to BRAF inhibitors. We demonstrate that Wnt5A and ROR2 expression is increased in BRAFV600E Vemurafenib (PLX 4032) resistant cell lines, and that ROR2 siRNA increases the sensitivity of these cell lines to therapy.

Our data indicate that the changes induced by the microenvironment can give rise to a subpopulation of highly invasive, therapy resistant cells. These data show that a single signaling pathway can effectively guide the phenotypic plasticity of a tumor cell, and is primed to do so by a changing microenvironment. This study demonstrates that the Wnt5A pathway is a prognostic marker for therapy response, necessary for the emergence of resistance, and may present a viable target for BRAF inhibitor adjuvant therapy.

Biography

Michael O'Connell received his Ph.D. from the University of Southampton (England) in collaboration with the University of Pennsylvania (USA). He completed his post-doctoral studies at the National Institute on Aging, part of the National Institutes of Health (NIH). Dr. O'Connell is a member of the American Association for Cancer Research (AACR) and the Society for Melanoma Research (SMR).

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