NDRG3-mediated lactate signaling in hypoxia

Kyung Chan Park1,*, Dong Chul Lee1,6 & Young Il Yeom1,2,*

1Genome Structure Research Center, 2Ochang Branch Institute, Korea Research Institute of Bioscience & Biotechnology (KRIBB), Daejeon 305-806, Korea

Hypoxia is associated with many pathological conditions as well as the normal physiology of metazoans. We identified a lactate-dependent signaling pathway in hypoxia, mediated by the oxygen- and lactate-regulated protein NDRG family member 3 (NDRG3). Oxygen negatively regulates NDRG3 expression at the protein level via the PHD2/VHL system, whereas lactate, produced in excess under prolonged hypoxia, blocks its proteasomal degradation by binding to NDRG3. We also found that the stabilized NDRG3 protein promotes angiogenesis and cell growth under hypoxia by activating the Raf-ERK pathway. Inhibiting cellular lactate production abolishes NDRG3-mediated hypoxia responses. The NDRG3-Raf-ERK axis therefore provides the genetic basis for lactate-induced hypoxia signaling, which can be exploited for the development of therapies targeting hypoxia-induced diseases in addition to advancing our understanding of the normal physiology of hypoxia responses.

Keywords: Hypoxia, Lactate signaling, NDRG3, HIF-independent hypoxia responses, PHD2/VHL pathway

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alternative energy source in oxidative tumors, as an inducer of angiogenesis, and as a modulator of cell motility. In line with these observations, high levels of lactate production and LDHA overexpression are known as negative prognostic markers in cancers. However, the key elements regulating the lactate-induced biologic responses and the underlying molecular mechanisms remain unknown.

Our results demonstrated the roles of lactate signaling in hypoxia as well as its genetic nature, which depends on the NDRG3-c-Raf-ERK1/2 axis. These findings suggest that HIF-1α and NDRG3 form an oxygen-dependent regulatory chain for hypoxia responses, divided into two chronological phases. At the early phase of hypoxia, HIF-1α protein accumulates, regulating the gene expression necessary for early adaptive responses including metabolic reprogramming, while at the later phase, the up-regulated lactate production signals for the accumulation of NDRG3, activating the Raf-ERK pathway to induce responses necessary for coping with prolonged hypoxia. Thus, the lactate signaling and accompanying biologic responses appear to be functionally coupled to the HIF-1α-induced metabolic reprogramming, employing NDRG3 as the critical link. In this regard, it is suggested that portions of the hypoxia responses, especially those occurring at the later phase of hypoxia, that have been so far attributed to HIF-1α, might, in fact, be under the direct control of NDRG3-mediated lactate signaling.

In conclusion, we demonstrated that NDRG3 functions as the hypoxia-inducible lactate sensor, playing key roles in the promotion of hypoxia responses in a HIF-independent manner. The role of NDRG3 in hypoxic lactate signaling implies that the PHD2/VHL system can control both HIF-dependent and -independent hypoxia responses in an oxygen-dependent manner. Therefore, the lactate-NDRG3-Raf-ERK signaling pathway may provide an extended mechanistic clue to the understanding of disorders caused by mutations in VHL (hemangioblastoma, renal cell carcinoma, pheochromocytoma, etc) or PHD2 (familial erythrocytosis-3) as well as the hypoxia-related physiological (differentiation and development, exercise physiology, etc) and pathophysiological responses (cancer, wound healing, inflammation, cardiovascular disorders, altitude sickness, etc). We also suggest that combinatorial targeting of HIF and NDRG3 might prove a highly effective anti-hypoxia strategy, considering the evidence indicating that simple inhibition of HIF may be insufficient for treating hypoxia-induced diseases.

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