Molecules and Cells

Editorial

The Multifaceted Roles for NRF2 in Regulating Tumor Development and Progression: An Update

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Nuclear factor E2-related factor 2 (NRF2) was originally identified as a master regulator of redox homeostasis and governs the expression of a group of genes involved in mitigating oxidative stress (Yamamoto et al., 2018). It also mediates the other types of adaptive survival responses, including those against electrophilic toxins (Kumagai et al., 2019) and inflammatory injury (Dinkova-Kostova and Copple, 2023; Kim and Surh, 2009).

The cellular stress response mediated by NRF2-induced cytoprotective signaling is often hijacked by cancer cells (de la Vega et al., 2018). This may facilitate the remodeling of the tumor microenvironment, thereby making it advantageous for the autonomic growth and metastasis of cancer cells, tumor angiogenesis, anticancer therapy resistance, and self-renewal activity of stem-like cells. Furthermore, recent studies have demonstrated the overactivation or overexpression of NRF2 in several different types of human malignancies, which contributes to tumor growth and progression through metabolic reprogramming (Hayes and Ashford, 2012; Mitsuishi et al., 2012).

This special issue of *Molecules and Cells* is intended to introduce cutting-edge research on the distinct effects of NRF2 on multi-stage carcinogenesis. The entire issue consists of five short seminal review articles written by world-renowned authorities in their related research field. First, Takafumi Suzuki et al. summarize the intracellular signaling pathways involved in the regulation of the KEAP1-NRF2 axis. These authors address the aberrant overactivation of NRF2 in various types of cancers with a poor prognosis, which is attributable to somatic mutations, epigenomic errors, exon skipping, etc. In this article, the "Cysteine Code" for the KEAP1 sensing of the electrophilic NRF2 inducers and "Hinge-Latch" model of the KEAP1-NRF2 interaction have been updated.

NRF2 also plays an important role in the cancer cell interactions with surrounding normal cells in the stroma of the tumor microenvironment. The second mini-review by Jialin Feng et al. highlights the emerging role of NRF2 in the tumor immune microenvironment (TIME). The NRF2 activation in tumor-associated macrophages can favor an anti-inflammatory and immunosuppressive TIME. In line with this concept, cancer cells can induce the polarization of tumor-associated macrophages toward an M2-like phenotype. The resulting cancer cell-educated macrophages activate the NRF2 in the cancer cells, which in turn induces the epithelial-mesenchymal transition (Feng et al., 2018). In contrast, elevated levels of NRF2 in myeloid-derived suppressor cells in the tumor microenvironment can suppress tumor development by reducing the accumulation of reactive oxygen species (ROS) in these cells (Hayashi et al., 2020; Satoh et al., 2010).

Cancer stem cells (CSCs), which are a small population of tumor cells characterized by their capacity for self-renewal and differentiation, possess enhanced capabilities to maintain reduced intracellular levels of ROS compared to the non-stem-like cancer cells. CSCs are currently postulated to be the driving force for intra-tumor heterogeneity, which accounts for the inherent resistance to chemo-, radio-, and immune-therapies. The third paper of this special issue written by Steffanus P. Hallis et al. describes the roles of NRF2

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signaling in conferring unique properties to CSCs with focus on their treatment resistance. Based on their own research (Choi et al., 2021) and others, the authors summarize the key NRF2-mediated signaling events required for the manifestation and maintenance of CSCs.

Ferroptosis is an iron- and lipid peroxidation-dependent form of cell death. Recent studies have indicated that NRF2 regulates the expression of genes controlling ferroptosis. By maintaining iron homeostasis and mitigating lipid peroxidation, NRF2 protects the cancer cells against ferroptotic cell death (Anandhan et al., 2023). By extending this finding, Aryatara Shakya et al. discuss the anti-ferroptic function of NRF2, which indicates the feasibility of inhibiting NRF2 to increase the intracellular labile iron pool and thus sensitize cancer cells to ferroptosis.

Considering the complex nature of the role of NRF2 as a pro- or anti-tumorigenic regulator of carcinogenesis, Christopher J. Occhiuto et al. address the differential effects of NRF2 on tumor initiation, promotion, and progression. These authors also emphasized the importance of the KEAP1-NRF2 axis in the tumor microenvironment and its regulation. The role of NRF2 in the development and progression of cancer is complex and context-dependent. A more precise landscape assessment of the different functions of NRF2 in the multistage carcinogenesis merits further exploration.

CONFLICT OF INTEREST

The authors have no potential conflicts of interest to disclose.

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