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Short communication

Cancer drug resistance: Links between carbonyl reducing enzymes and kinase inhibitors

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Introduction

Resistance to anticancer therapies remains one of the major challenges in oncology. While targeted kinase inhibitors have significantly improved outcomes in various malignancies, both intrinsic and acquired resistance frequently limit their long-term efficacy. Among the mechanisms contributing to resistance, metabolic adaptations within tumor cells have gained increasing attention. Carbonyl reducing enzymes (CREs), including members of the aldo-keto reductase (AKR) and short-chain dehydrogenase/reductase (SDR) superfamilies, participate in the detoxification of reactive carbonyl compounds and the metabolism of endogenous and exogenous substrates. Recent evidence suggests that altered CRE expression may influence cellular responses to kinase inhibitors by modulating oxidative stress, drug metabolism, and survival signaling pathways. This short communication summarizes current evidence linking CREs to resistance mechanisms associated with kinase-targeted therapies.

Carbonyl reducing enzymes in cancer biology

CREs catalyze the NAD(P)H-dependent reduction of aldehydes and ketones into less reactive alcohols. Major representatives include AKR1A1, 1B1, 1B10, 1C3, 7A2, carbonyl reductase 1 (CBR1), and related reductases. In cancer cells, these enzymes contribute to protection against oxidative damage by detoxifying reactive aldehydes generated during lipid peroxidation and cellular stress.

Numerous studies have reported elevated expression of AKR and CBR family members in solid tumors and hematological malignancies. Increased CRE activity has been associated with enhanced proliferation, resistance to apoptosis, and adaptation to hostile tumor microenvironments. Furthermore, CREs can influence the metabolism of anticancer drugs, thereby altering intracellular drug concentrations and therapeutic responses (Penning et al., 2021).

Kinase inhibitors and mechanisms of resistance

Protein kinase inhibitors target key oncogenic signaling pathways, including EGFR, BCR-ABL, ALK, VEGFR, and PI3K/AKT/mTOR networks. Despite remarkable clinical success, resistance often emerges through secondary mutations, activation of bypass pathways, epigenetic changes, or metabolic reprogramming (Yang et al., 2022).

Cancer cells exposed to kinase inhibitors frequently experience increased oxidative stress. To survive, they activate antioxidant and detoxification systems regulated by transcription factors such as

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NRF2. Because the genes encoding many CREs are NRF2-responsive, their expression may increase during treatment. Elevated CRE activity can support cell survival by reducing toxic carbonyl species and maintaining redox homeostasis, thereby diminishing the cytotoxic effects of kinase inhibition.

Emerging links between carbonyl reducing enzymes and kinase inhibitor resistance

Recent research suggests that CREs may contribute directly or indirectly to resistance to kinase inhibitors. For example, overexpression of AKR1C family enzymes has been observed in resistant cancer cell lines and has been linked to enhanced antioxidant capacity. By lowering oxidative stress and preventing apoptosis, these enzymes may allow tumor cells to tolerate prolonged kinase inhibition (Zhou et al., 2021).

In addition, kinase signaling pathways can regulate CRE expression. Activation of PI3K/AKT, MAPK, and NRF2-related networks influences transcription of AKR and CBR genes, creating feedback loops that promote drug tolerance. Some studies have also suggested that inhibition of AKR1C enzymes can restore sensitivity to targeted therapies, highlighting CREs as potential therapeutic targets (Wu et al., 2022).

Although the precise molecular mechanisms remain incompletely understood, current evidence supports the concept that CREs participate in a broader adaptive response that enables cancer cells to survive kinase-targeted treatment. Further investigation is needed to determine whether CRE expression can serve as a predictive biomarker or therapeutic vulnerability in resistant tumors.

Conclusion

CREs are increasingly recognized as important contributors to cancer cell adaptation and drug resistance. Through their roles in detoxification, redox regulation, and interaction with oncogenic signaling pathways, these enzymes may influence the effectiveness of kinase inhibitors. Understanding the interplay between CREs and targeted therapies could provide new opportunities for overcoming resistance and improving clinical outcomes. Future studies should focus on clarifying the molecular connections between specific reductases and kinase signaling networks, as well as evaluating CRE inhibitors in combination with established targeted therapies.

References

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