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Review

Therapeutic targeting of oncogenic transcription factors by natural products in eye cancer

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ABSTRACT

Carcinogenesis has a multifactorial etiology, and the underlying molecular pathogenesis is still not entirely understood, especially for eye cancers. Primary malignant intraocular neoplasms are relatively rare, but delayed detection and inappropriate management contribute to poor outcomes. Conventional treatment, such as orbital exenteration, chemotherapy, or radiotherapy, alone results in high mortality for many of these malignancies. Recent sequential multimodal therapy with a combination of high-dose chemotherapy, followed by appropriate surgery, radiotherapy, and additional adjuvant chemotherapy has helped dramatically improve management. Transcription factors are proteins that regulate gene expression by modulating the synthesis of mRNA. Since transcription is a dominant control point in the production of many proteins, transcription factors represent key regulators for numerous cellular functions, including proliferation, differentiation, and apoptosis, making them compelling targets for drug development. Natural compounds have been studied for their potential to be potent yet safe chemotherapeutic drugs. Since the ancient times, plant-derived bioactive molecules have been used to treat dreadful diseases like cancer, and several refined pharmaceutics have been developed from these compounds. Understanding targeting mechanisms of oncogenic transcription factors by natural products can add to our oncologic management toolbox. This review summarizes the current findings of natural products in targeting specific oncogenic transcription factors in various types of eye cancer.

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Contents

Abbreviations: 2,5-DXP, 2,5-diketopiperazine; ACC, adenoid cystic carcinomas; BBR, berberine; BET, bromodomain and extraterminal; CA, chebulagic acid; CPT, camptothecin; EMT, epithelial-mesenchymal transition; GSK3, glycogen synthase kinase 3-; HCC, hepatocellular carcinoma; HDAC, histone deacetylases; Hh, hedgehog; HIF-1, hypoxic inducible factor 1; IkB, Inhibitor of NFkB; IKK, IkB kinase; ISJ, Isojacareubin; JapA, Japonicones A; LGACC, lacrimal gland adenocystic carcinoma; LinA, linearifolianoid A; MAPK, mitogen-activated protein kinase; NFkB, nuclear Factor kB; PKC, protein kinase C; PRAME, preferentially expressed antigen in melanoma; pVHL, von hippel-lindau tumor suppressor; RB, retinoblastoma; SCC, sebaceous cell carcinoma; Shh, sonic hedgehog; Smo, smoothened; TCF/LEF, T-cell factor/leukocyte enhancer factor; TEAD, TEA domain; Topo1, topoisomerase I; TPT, topotecan; UM, uveal melanoma; UTR, untranslated region; YAP, yes-associated proteins.

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1. Introduction

Natural products have been used on an empirical basis for healing throughout history. According to the World Health Organization in 2008, more than 80% of the world's population relies on traditional, ethnobotanical medicines for their primary healthcare needs [1,2]. Studies of biologically active components from natural products derived from plants, animals, and microbes have led to several advancements in medical therapies. Before the chemist Felix Hoffman at Bayer developed aspirin, the ancient Egyptians and Greeks treated pain with willow leaves and bark, which contain the active component used to derive aspirin [3]. Lately, natural products have received considerable attention for their anticancer activity. As a matter fact, 74.9% of anticancer drugs (excluding vaccines and biologicals) developed between the 1940s and 2010 are naturally derived or inspired [2]. Active components from natural compounds, such as alkaloids, taxanes, and flavonoids have been utilized to develop chemotherapeutic drugs to treat various cancers such as leukemia, breast, prostate, and ovarian cancer [4–9].

While natural compounds are used to treat various cancers or are currently in clinical trials, research regarding the application of natural products to the treatment of ocular cancer is lacking. This is most likely due to the rarity of ocular cancers. Previous epidemiological studies of Western populations suggest that eye cancers account for about 0.2% of cancer diagnoses and less than 0.1% of cancer deaths [10,11]. However, while rare, they greatly diminish quality of life and are deadly if left untreated. The most common adult intraocular cancer is uveal melanoma, and it is the most lethal melanoma with survival rates at 50% over a 10-year period [12]. The most common pediatric intraocular cancer is retinoblastoma, and the first-line treatment for Grade I–IV retinoblastoma according to the International Retinoblastoma Staging System (IRSS) is enucleation, leading to irreversible blindness [13].

There is much overlap in the mechanisms underlying the various types of cancers. Overexpression of oncogenes and inactivation of tumor suppressor genes are typically the initiating events in tumor development [14–17]. Some of these genetic and epigenetic events involve genes encoding transcription factors, which bind to specific DNA elements and regulate several gene expression patterns. Three groups of transcription factors are known to play important roles in cancer [18]. The group first recognized is the steroid receptors (e.g. estrogen receptors in breast cancer and androgen receptors in prostate cancer) [19]. The second group identified is resident nuclear proteins, normally activated by serine kinase cascades [20]. And the most recently recognized group is the latent cytoplasmic factors, normally activated by receptor–ligand interaction at the cell surface [21]. Multiple dysregulated genes converge to specific sets of transcription factors, and interference at these transcription factors is highly desirable in drug development [21–24].

Natural products of plants and microbes offer an important and largely unexplored pool for the identification and development of novel drugs. They are exceptionally diverse and can produce a variety of secondary metabolites that have therapeutic functions. It is estimated that only 6% of identified plant species have been systematically investigated pharmacologically [25]. Additionally, microbes, such as endophytic bacteria, are able to biosynthesize some anti-cancer metabolites, hosting a reservoir of potentially therapeutic compounds. The vast microbial diversity has great potential for the discovery of new drug leads. Thus, natural products are an untapped potential that can lead to the development of better, safer and more effective anticancer drugs.

Research regarding natural products for treating ocular cancers is limited. By discussing key ocular oncogenic transcription factors and pathways in eye cancer and the natural agents known to affect these same pathways in other cancers, we hope the consolidated information will be used for future translational research in ocular oncology drug discovery. While some pathways are important in multiple ocular cancers, in this review, we summarize current findings of natural products that target the pathways most pertinent to each different type of eye cancer. Elucidating natural products' effects on directly or indirectly modulating oncogenic factors may enhance our development of better pharmaceutical scaffolds and new targeted therapies for the management of ocular tumors (Fig. 1) [11].

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