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The interplay of NR4A receptors and the oncogene–tumor suppressor networks in cancer

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ABSTRACT

Nuclear receptor (NR) subfamily 4 group A (NR4A) is a family of three highly homologous orphan nuclear receptors that have multiple physiological and pathological roles, including some in cancer. These NRs are reportedly dysregulated in multiple cancer types, with many studies demonstrating pro-oncogenic roles for NR4A1 (Nur77) and NR4A2 (Nurr1). Additionally, NR4A1 and NR4A3 (Nor-1) are described as tumor suppressors in leukemia. The dysregulation and functions of the NR4A members are due to many factors, including transcriptional regulation, protein-protein interactions, and post-translational modifications. These various levels of intracellular regulation result from the signaling cross-talk of the NR4A members with various signaling pathways, many of which are relevant to cancer and likely explain the family members' functions in oncogenesis and tumor suppression. In this review, we discuss the multiple functions of the NR4A receptors in cancer and summarize a growing body of scientific literature that describes the interconnectedness of the NR4A receptors with various oncogene and tumor suppressor pathways.

1. Introduction

The human nuclear receptor (NR) family is a group of structurally related transcription factors that regulate specific gene expression in a ligand-dependent manner. This superfamily of receptors constitutes an important group of drug targets that are useful in identifying compounds that affect a wide range of physiological and pathological events [1]. NRs share a common structural arrangement that consists of an N-terminal domain containing an activation function–1 (AF-1) region, a DNA-binding domain, a hinge region, and a C-terminal ligand-binding domain (LBD) that can also encode an AF-2 domain. NR subfamily 4 group A (NR4A) is composed of three members: Nur77 (NR4A1, also known as nerve growth factor IB or NGFIB), Nurr1 (NR4A2), and Nor-1 (NR4A3).

Members of the NR4A subgroup respond to various stimuli, and their expression can be induced by mitogens, stress, and apoptotic signals, implicating their roles in multiple biological processes [2,3]. The NR4A receptors are classified as orphan receptors, having no known physiological ligands, and do not contain a typical ligand-binding domain structure common to other NRs [2,4–6] although recent evidence suggests that unsaturated fatty acid metabolites could serve as the missing ligand for Nur77 [7]. Typical NRs have a ligand-binding domain containing a hydrophobic cleft for ligand- and coactivator-binding, but structural studies show that the NR4A subgroup contains an atypical ligand-binding groove that is hindered by bulky side groups of hydrophobic residues. Thus, the NR4A receptors are believed to be regulated in a ligand-independent manner, and a growing amount of literature supports the notion that these receptors are regulated largely by post-translational modifications and protein-protein interactions and that their expression and localization within the cell influence their cellular functions.

2. NR4A receptors in cancer

The NR4A receptors promote or suppress tumors depending on specific cellular context. For example, Nur77 is overexpressed in cancer cell and tissue samples of multiple origins, causing increased proliferation and survival in these cells and tissues [8] at least partly via upregulation of several target genes, including cyclin D2 [9], *E2F1* [10], survivin [11], and thioredoxin domain–containing 5 (*TXNDC5*) [12], which are mediators of cell cycle progression, apoptotic inhibition and reactive oxygen species (ROS) regulation (Fig. 1). In addition, loss-of-function studies of Nur77 have demonstrated its importance in cell proliferation and survival [13], with the consensus being that Nur77 knockdown reduces cellular proliferation and angiogenesis and induces intrinsic and extrinsic apoptotic pathways. It is important to note that many loss-of-function studies are performed on non-stimulated cells to determine the role of basal, endogenous Nur77. Conversely, in cells stimulated with various apoptosis-inducing agents, Nur77 plays a role in cell death through both transcription-dependent and -independent mechanisms (Fig. 1).

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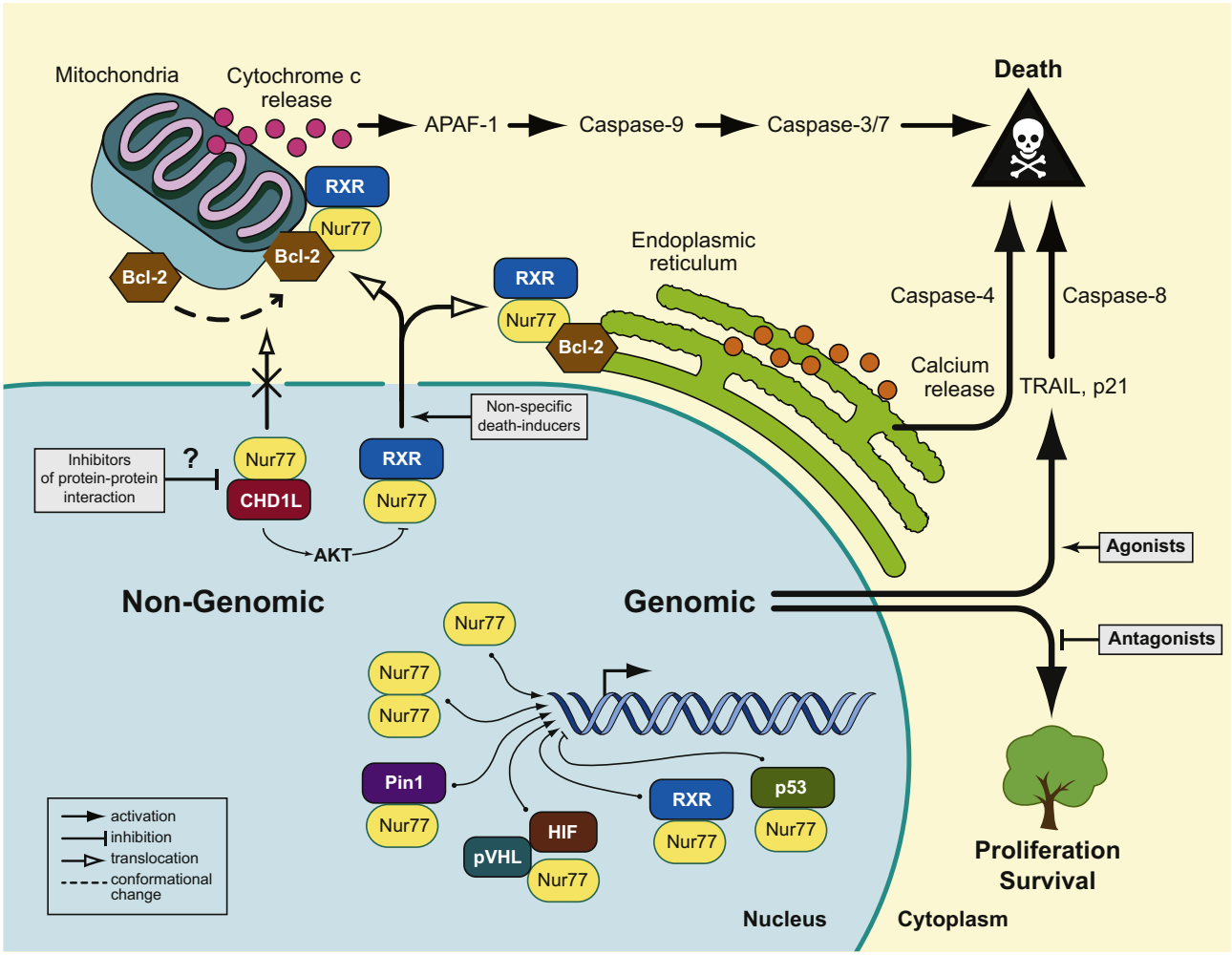

Fig. 1. Nur77 mediates cell death or survival through localization-dependent and -independent mechanisms. As a nuclear transcription factor, Nur77 largely promotes cell proliferation and survival through regulation of specific target genes (i.e., cyclin D2, E2F1, survivin, TXNDC5), which can be impeded by NR4A antagonists. Additionally, some agonists of Nur77 transactivation are able to mediate transcription-dependent cell death. A major mechanism of Nur77-mediated cell death is the nuclear export of Nur77-RXRα heterodimers, which is suppressed by the *CHD1L* oncogene. Cytoplasmic Nur77 can activate mitochondrial- or ER-associated cell death by interacting with membrane-bound Bcl-2.

Because of the dual and opposite roles of Nur77 in cell proliferation and death, many studies have been focused on therapeutically targeting Nur77 to impede its oncogenic functions while coaxing it to activate the cellular death program [14]. These efforts would rely on the fact that non-tumor tissue will express Nur77 at much lower levels, making these tissues less responsive to Nur77-mediated apoptosis-inducing agents.

Nurr1 has been implicated in cancer progression although its cancer-related target genes have not been characterized. Nurr1 knockdown decreases anchorage-independent growth, suggesting that Nurr1 plays a role in cell transformation [15,16]. The protein promotes migration but not overall proliferation in bladder cancer [17], although it does affect cell proliferation in lung and breast cancer [18,19]. Nurr1 expression is higher in squamous cell carcinoma (SCC) samples than in normal tissues of patients with SCC, and induction of Nurr1 expression in SCC leads to increased resistance to 5-fluorouracil [20], suggesting a role for Nurr1 in drug resistance [20,21]. Additionally, Nurr1 overexpression contributes to protection from doxorubicin-induced apoptosis by diminishing the p53 response [22].

In patients with breast cancer, Nurr1 expression in normal breast epithelium is higher than that in tumor tissue and has been positively correlated with favorable prognosis [19]. Conversely, the same study found that knockdown of Nurr1 in breast cancer cell lines diminished xenograft tumor growth. The different roles of Nurr1 in different tissues point to possible context-dependent effects of Nurr1, which might also depend on the intracellular localization of Nurr1 protein, as cytoplasmic expression of Nurr1 in bladder cancer was correlated with decreased patient survival [17]. However, other studies using either stimulated endogenous or overexpressed exogenous Nurr1 have not clearly determined its subcellular localization.

Less is known about Nor-1's functions in cancer, although some key findings have been made. For example, *Nr4a1*$^{-/-}$;*Nr4a3*$^{-/-}$ double-knockout mice develop acute myeloid leukemia (AML) with very rapid onset, dying within 2 to 4 weeks postnatally [23]. The myeloid cells from these mice have more S- and G2/M-phase populations and fewer annexin V–positive cells than do those of wild-type mice. The decrease in apoptotic cells was attributed to a reduction in extrinsic cell death signaling, as indicated by a decrease in Fas ligand and *TRAIL* expression. Expression of Nur77 and Nor-1 were dramatically reduced in AML patient samples. Together, these data suggest that these two NR4A receptors can play overlapping tumor suppressive roles in leukemia, as NR4A single-knockout mice do not develop cancer [24,25]. The functional redundancy of Nur77 and Nor-1 was further confirmed in a follow-up study investigating genome-wide transcriptional changes in response to NR4A restoration in AML [26]. Nur77 and Nor-1 shared overlapping gene signatures by regulating 97% of the same transcripts, and re-expression of either NR4A receptor was able to elicit tumor-suppressive functions by reducing proliferation and increasing apoptosis. Furthermore, NR4A re-expression suppressed *MYC* and its accompanying oncogenic signature in multiple AML cells.