RELATIONSHIP BETWEEN *MycN* COPY NUMBER AND EXPRESSION IN RHABDOMYOSARCOMAS AND CORRELATION WITH ADVERSE PROGNOSIS IN THE ALVEOLAR SUBTYPE

Williamson D, Lu YJ, Gordon T, et al
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Amplification of the transcription factor *MycN* is an important molecular diagnostic tool in stratifying treatment for neuroblastoma. Increased copy number and overexpression of *MycN* in rhabdomyosarcoma has been described in a number of small studies with conflicting conclusions about its association with clinicopathologic characteristics. The authors aimed to study the phenomenon in the largest series to date.
Using quantitative polymerase chain reaction, they measured *MycN* copy number and expression levels in rhabdomyosarcoma samples from 113 and 92 individuals with a confirmed diagnosis of rhabdomyosarcoma, respectively.
Increased copy number of *MycN* was found to be a feature of both the embryonal and alveolar subtypes. The copy number and expression levels were significantly greater in the alveolar subtype, although the range of expression in both subtypes spanned several orders of magnitude. *MycN* copy number showed a significant correlation with expression in the alveolar subtype. It is notable that relatively high expression frequently occurred in embryonal rhabdomyosarcoma without high copy number and that low expression was found in some cases with high copy number. In patients with alveolar rhabdomyosarcoma, overexpression or gain of genomic copies of *MycN* were significantly associated with adverse outcome.
In conclusion, *MycN* deregulation is a feature of rhabdomyosarcoma tumorigenesis, defines groups of patients with a poor prognosis, and is a potential target for novel therapies.

UP-REGULATION OF CXCR4 IS ESSENTIAL FOR HER2-MEDIATED TUMOR METASTASIS

Li YM, Pan Y, Wei Y, et al
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HER2 a member of the epidermal growth factor family is over-expressed in a large number of cancers, including 30% of breast cancers and it is an important target in breast cancer therapy. HER2 over-expression seems also to play an important role in promoting metastasis although the mechanism involved is poorly understood. In this manuscript Li and colleagues identified CXCR4 as a target of HER2. CXCR4 is a G-protein coupled receptor previously implicated in breast cancer metastasis. The authors demonstrated that overexpresssion of HER2 in breast cancer cells increases expression of CXCR4. Inhibition of HER2 expression by RNAi or inhibition of HER2 by trastuzumab treatment results in reduction of CXCR4 expression. The mechanisms of induction of CXCR4 expression by HER2, involves the PI3K/Akt/mTOR signaling pathway. In human breast cancer biopsy samples, the authors found that expression of CXCR4 correlates with Her2 expression and a bad prognosis. The results showed by Li and coworkers indicate that targeting the CXCR4 pathway (that includes the CXCR4 ligand CXCL12) and also HER2 should improve survival of breast cancer patients in HER2 positive tumors.

IDENTIFICATION OF OTX2, AS A MEDULLOBLASTOMA ONCOGENE, WHOSE PRODUCT CAN BE TARGETED BY ALL-TRANS RETINOIC ACID.

Di C, Liao S, Adamson DC, et al
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OTX2 is a member of a highly conserved family containing the bicoid-like homeodomain transcription factors that control the developmental programs that direct morphogenesis. In this article Di and colleagues have found an essential role of OTX2 expression in the generation of medulloblastoma. By digital kariotyping of medulloblastoma cell lines that authors found that OTX2 was amplified more that three fold in some cell lines. OTX2 transcripts were found elevated in 93% of medulloblastoma cell lines with aplastic histopathological features. In these cells, inhibition of OTX2 expression by RNAi inhibited medulloblastoma cell growth. Retinoids, have been shown to inhibit OTX2 expression in embryonic neurons system thorough cis- acting elements of the OTX2 promoter. The authors found that all-trans-retinoic acid (ATRA) abrogated cell proliferation in all the OTX2 expressing cell lines, but had no growth inhibitory effects on those medulloblastoma cell lines that expressed OTX2 at low levels. On OTX2 expressing cells, inhibition of cell growth was prominently due to apoptosis induction. This study indicates that a rational use of a new therapeutic agent against medulloblastoma should be considered for clinical studies.