Neuroblastoma are malignant pediatric tumors with a low mutation frequency. Recurrent alterations include MYCN amplification and ATRX mutation. Although in about half of cases tumors spontaneously regress or are cured by limited therapy, the remaining cases have poorer outcomes, and the molecular mechanisms that drive high-risk neuroblastoma are not well understood. To characterize structural alterations in high-risk neuroblastoma, Peifer and colleagues performed whole-genome sequencing of 56 neuroblastoma tumors and matched normal controls, which identified four recurrent breakpoint clusters. Three of these clusters were related to known genetic alterations, whereas the fourth was in chromosome 5p15.33 upstream of the telomerase reverse transcriptase (TERT) gene. These latter rearrangements occurred in 21% of tumors and were structurally diverse, including balanced translocations, copy-number gains, high-level amplifications, and chromothripsis; however, these rearrangements did not directly affect the TERT gene or its promoter. TERT rearrangements were exclusively found in high-risk neuroblastomas, mutually exclusive to ATRX and MYCN alterations, and associated with a poor patient outcome and high expression of TERT mRNA. MYCN-amplified tumors also showed high TERT expression, and MYCN knockdown downregulated TERT, suggesting that 5p15.33 rearrangement and MYCN amplification both confer high risk through TERT activation. Chromatin immunoprecipitation sequencing in TERT-rearranged tumors indicated that active enhancer histone modifications were clustered immediately next to the breakpoints, suggesting that rearrangement juxtaposed TERT to strong enhancer elements and induced epigenetic remodeling of the TERT locus. Mechanistically, the high levels of TERT expression were associated with an increase in telomerase activity in TERT-rearranged and MYCN-amplified tumors, which led to telomere shortening, whereas in ATRX-mutant or other high-risk tumors lacking TERT or MYCN alterations the alternative lengthening of telomeres (ALT) pathway was activated. Altogether, this study identifies recurrent TERT rearrangement and telomere shortening as an important mechanism characterizing high-risk tumors and supports the development of telomerase inhibitors to treat this aggressive disease.


Metastasis

Major finding: TGFβ released in metastasis-associated bone destruction contributes to skeletal muscle weakness.

Mechanism: Excess TGFβ upregulates NOX4, resulting in RYR1 oxidation and intracellular Ca2+ leakage.

Impact: Targeting TGFβ, NOX4, or RYR1 may reduce skeletal muscle weakness associated with bone metastases.

TGFβ REGULATES BONE METASTASIS-ASSOCIATED SKELETAL MUSCLE WEAKNESS

Patients with advanced cancer often develop bone metastases, which secrete factors that induce osteoclastic bone resorption and lead to the release of bone matrix growth factors, including TGFβ, which promote tumor growth and osteolysis. Bone metastases are also often associated with debilitating skeletal muscle weakness, for which there is no effective treatment. Research has focused on increasing muscle mass in patients, but it is unclear whether increased muscle mass is sufficient to improve muscle function. Waning, Mohammad, and colleagues showed that TGFβ activity mediates metastasis-related skeletal muscle weakness using mouse models of advanced human cancers that are often associated with bone metastases and muscle weakness, including breast, prostate, and lung cancers and multiple myeloma. Mice with osteolytic bone metastases exhibited decreased muscle function and increased oxidation of skeletal muscle proteins, in particular the ryanodine receptor 1 (RYR1) calcium (Ca2+) release channel. RYR1 oxidation was also detected in humans with cancer-associated bone metastases and resulted in pathologic leaking of Ca2+ from the sarcoplasmic reticulum, which contributes to muscle weakness. In contrast, mice with mammary tumors without bone metastases had normal muscle function and no Ca2+ leakage from RYR1 channels. Further, preventing RYR1 Ca2+ release with the channel stabilizer Rycal (S107) improved muscle strength without affecting muscle mass, indicating that loss of muscle mass does not fully explain the muscle weakness associated with bone metastases. Likewise, TGFβ inhibition enhanced muscle strength, whereas TGFβ treatment was sufficient to trigger RYR1 channel remodeling and intracellular Ca2+ leakage via induction of NADPH oxidase 4 (NOX4) and increased interaction of NOX4 with RYR1, leading to RYR1 oxidation. These findings suggest that cancer-associated skeletal muscle weakness is induced by osteolysis and the resulting increase in TGFβ activity in the tumor-bone microenvironment. Targeting TGFβ (or its release from bone by blocking bone destruction), NOX4, or RYR1 might help to alleviate skeletal muscle weakness in patients with bone metastases.


TERT REARRANGEMENT ACTIVATES TELOMERASE IN HIGH-RISK NEUROBLASTOMA

Neuroblastomas are malignant pediatric tumors with a low mutation frequency. Recurrent alterations include MYCN amplification and ATRX mutation. Although in about half of cases tumors spontaneously regress or are cured by limited therapy, the remaining cases have poorer outcomes, and the molecular mechanisms that drive high-risk neuroblastoma are not well understood. To characterize structural alterations in high-risk neuroblastoma, Peifer and colleagues performed whole-genome sequencing of 56 neuroblastoma tumors and matched normal controls, which identified four recurrent breakpoint clusters. Three of these clusters were related to known genetic alterations, whereas the fourth was in chromosome 5p15.33 upstream of the telomerase reverse transcriptase (TERT) gene. These latter rearrangements occurred in 21% of tumors and were structurally diverse, including balanced translocations, copy-number gains, high-level amplifications, and chromothripsis; however, these rearrangements did not directly affect the TERT gene or its promoter. TERT rearrangements were exclusively found in high-risk neuroblastomas, mutually exclusive to ATRX and MYCN alterations, and associated with a poor patient outcome and high expression of TERT mRNA. MYCN-amplified tumors also showed high TERT expression, and MYCN knockdown downregulated TERT, suggesting that 5p15.33 rearrangement and MYCN amplification both confer high risk through TERT activation. Chromatin immunoprecipitation sequencing in TERT-rearranged tumors indicated that active enhancer histone modifications were clustered immediately next to the breakpoints, suggesting that rearrangement juxtaposed TERT to strong enhancer elements and induced epigenetic remodeling of the TERT locus. Mechanistically, the high levels of TERT expression were associated with an increase in telomerase activity in TERT-rearranged and MYCN-amplified tumors, which led to telomere shortening, whereas in ATRX-mutant or other high-risk tumors lacking TERT or MYCN alterations the alternative lengthening of telomeres (ALT) pathway was activated. Altogether, this study identifies recurrent TERT rearrangement and telomere shortening as an important mechanism characterizing high-risk tumors and supports the development of telomerase inhibitors to treat this aggressive disease.

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