How to target the ultra-high-risk neuroblatoma?

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The prognosis of neuroblastoma (NB) has significantly improved for the last decades according to the development of multidisciplinary therapy. However, the outcome of the patients with high-risk NB is still poor. Based on our data set in Japan, the 10-year overall survival rate of stage 4 NB, which covers about a half of NB, showed 41% (n=282). In addition, it is getting obvious that NB in stage 4 is highly heterogeneous in its biology and genetics and shows variable survival rates. Therefore, we need to identify a specific group of NB possessing ultra-high-risk characteristics to improve the prognosis as well as to achieve the precision medicine of NB.

The International NB Risk Group (INRG) has recently published an improved risk grouping. However, since it does not include ultra-high-risk NB group, we challenged to identify such group of NB.

Our analyses showed that array CGH-based genome subgroup P2a and P2s (both with 1p loss, 11q loss and 17q gain) with and without MYCN amplification showed ultra-high-risk phenotype of NB. The methylome analysis also indicated that Ps tumors can be clearly divided into four clusters, two of which showed high-risk or ultra-high-risk phenotype. Furthermore, our study suggested that genomic landscape, including the three transcription factors-related networks (DNA-damage response, RB and TP53 mutations) and the mutations in chromatin remodeling/regulating genes, seems to be very helpful to indentify the ultra-high-risk of NB. Thus, the combination of “methylome profile” may be useful for defining the ultra-high-risk group of NB to construct new therapeutic strategies especially in the subsets without MYCN amplification.

As for the therapies against ultra-high-risk NB, new target molecules, novel immunotherapies, new chemotherapeutic reagents, innovative particle beam radiation therapy, etc. will be discussed.