p53, stem cell biology and childhood blastomas

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Purpose of review
Childhood blastomas, unlike adult cancers, originate from developing organs in which molecular and cellular features exhibit differentiation arrest and embryonic characteristics. Conventional cancer therapies, which rely on the generalized cytotoxic effect on rapidly dividing cells, may damage delicate organs in young children, leading to multiple late effects. Deep understanding of the biology of embryonal cancers is crucial in reshaping the cancer treatment paradigm for children.

Recent findings
p53 plays a major physiological role in embryonic development, by controlling cell proliferation, differentiation and responses to cellular stress. Tumor suppressor function of p53 is commonly lost in adult cancers through genetic alterations. However, both somatic and germline p53 mutations are rare in childhood blastomas, suggesting that in these cancers, p53 may be inactivated through other mechanisms than mutation. In this review, we summarize current knowledge about p53 pathway inactivation in childhood blastomas (specifically neuroblastoma, retinoblastoma and Wilms’ tumor) through various upstream mechanisms. Laboratory evidence and clinical trials of targeted therapies specific to exploiting p53 upstream regulators are discussed.

Summary
Despite the low rate of inherent TP53 mutations, p53 pathway inactivation is a common denominator in childhood blastomas. Exploiting p53 and its regulators is likely to translate into more effective targeted therapies with minimal late effects for children. (See Video Abstract, Supplemental Digital Content 1, http://links.lww.com/COON/A23).

Keywords
childhood blastomas, differentiation, p53, stem cells, targeted therapy

INTRODUCTION
Blastomas are a heterogeneous group of primitive neoplasms, more common in children than in adults, where tumor cells are composed of immature undifferentiated cells resembling those of the blastoma or primordium of the organ in which the tumor arises. Examples of childhood blastoma include neuroblastoma, nephroblastoma (Wilms’ tumor), retinoblastoma, hepatoblastoma and several very rare forms, namely pleuropulmonary blastoma and pancreaticoblastoma [1]. These cancers, sometimes referred to as ‘embryonal cancers,’ are predominantly located in developing tissues of children younger than 4 years [2]. They are postulated to arise from embryonic cells that fail to undergo normal maturation during development [3]. Collectively, the age-standardized incidence rates of embryonal cancers in the United States and Europe are estimated to about 5.5 per million (2.4 neuroblastoma, 1.9 Wilms’ tumor, 0.8 retinoblastoma and less than 0.5 for other types). Survival rates are generally high (greater than 90% for Wilms’ tumor and retinoblastoma, 71% for hepatoblastoma, 68% for neuroblastoma) with the best outcome seen in children aged 0–14 years [2]. However, certain subtypes have much lower survival rates despite intensive treatment. For example, high-risk neuroblastoma is highly lethal, with a 5-year overall survival of only 40–50% [4].

A recent analysis of the landscape of genomic alterations across 24 types of childhood cancers has revealed marked differences in terms of mutation frequency and significantly mutated genes (SMGs) in comparison with most adult cancers [5*]. This analysis has shown that mutation frequencies in childhood cancers ranged between 0.02 and 0.49.

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