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Review Article

Unresolved Questions in Hepatoblastoma

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Abstract

Despite being the least molecularly complex of all human cancers, hepatoblastoma (HB), the most common pediatric liver malignancy, shows substantial phenotypic and transcriptional diversity. Recent studies have established that this originates from different combinations of the 3 pro-oncogenic transcription factors that are most frequently deregulated in these tumors: β-catenin, YAP and NFE2L2 and that additional diversity can be imparted by different β-catenin mutants. These findings raise questions as to whether the current practice of employing identical drug combinations to treat all HBs, without regard for their molecular landscapes, represents the best approach and whether chemo-resistance develops similarly in these different backgrounds. While these questions are best addressed in immortalized cell lines representative of each molecular subtype, such HB cell lines do not currently exist. However, new murine cell lines that meet these criteria are currently under development and should soon allow us to address these clinically relevant issues.

Keywords: β-catenin, Hepatocellular carcinoma, Hippo, NFE2L2, NRF2, Wnt, YAP

Introduction

Hepatoblastoma (HB) is the most common pediatric liver cancer, with about 100-200 new cases per year being diagnosed in the United States, nearly all of which occur in children <4 years of age [1]. The increasing incidence of HB has been attributed to the improved survival of low-birth-weight infants or those born prematurely, groups that are particularly susceptible to developing the tumor [2]. Certain genetic disorders also predispose to the development of HB, including Beckwith-Wiedemann and Li-Fraumeni syndromes, hemi-hypertrophy, and Familial Adenomatous Polyposis (FAP) where the incidence has been estimated to be as much as 5000-7000-fold greater than normal [1-5]. At least 7 distinct histologic HB sub-types have been identified and some of these are predictive of survival [6,7]. Other prognostic factors include patient age and race, the presence of multiple tumors, and serum alpha feto-protein levels [2,8].

Despite the rarity of the tumor and the ~70% cure rate for affected individuals, the disease exerts disproportionate burdens, medical and otherwise, upon patients and their families for a number of reasons. These include the life-long health consequences of the cytotoxic chemotherapies used to treat HB, particularly among such a young cohort. Orthotopic Liver Transplantation (OLT), which is currently the only curative option for recurrent disease, exerts its own long-term challenges including the need for life-long immune suppression and its own consequences that include the high risk of infection and the development of second malignancies [9]. The chronic care these individuals require and the long- term side effects they must endure also exert significant economic, psychological, and social burdens upon them and their families [10,11]. The need to maximize the most effective and least toxic therapies, to discover new ones and to individualize or "personalize" these therapies are demands that continue to confront and motivate those who care for these patients.

Molecular Drivers of HB

Most childhood cancers are molecularly uncomplicated compared to adult cancers and this is especially true for HBs, which are the least complex of all human cancers [12,13]. Over the past several years, 3 major oncogenic signaling pathways have been identified

as being recurrently de-regulated in most HB cases: the Wnt/β-catenin, Hippo and NFE2L2/NRF pathways.

The Wnt/β-Catenin Pathway

Several groups have identified heterogeneous missense and in-frame deletions in the CTNNB1 gene, which encodes β-catenin, the pathway's terminal transcription factor [3,14-16]. Numerous studies have confirmed these findings and identified mutation frequencies as high as 80% [17,18]. Despite the diversity of the mutations that have been identified, they are overwhelmingly confined to the region of β-catenin encoded by exon 3 [14,17,18]. This region is critical for β-catenin's interaction with the APC tumor suppressor complex, which constrains it in a transcriptionally inactive form in the cytoplasm until Wnt signaling promotes its dissociation and subsequent trafficking to the nucleus. As a result, a large proportion of HBs demonstrate constitutive nuclear localization of β-catenin [14,17-19].

The Hippo Pathway

Although no defined recurrent mutations within the Hippo pathway have been defined as they have for β-catenin, the pathway is clearly activated in a significant number of HB cases, which commonly show evidence for nuclear localization and accumulation of YAP, the pathway's terminal transcription factor [17,20].

The NFE2L2/NRF2 Pathway

As many as 50% of HBs are associated with missense mutations in or amplification of the *NFE2L2* gene, which encodes a transcription factor that responds to and is responsible for mediating the response to oxidative stress [21,22]. Reminiscent of β-catenin's regulation, *NFE2L2* is normally retained in the cytoplasm in an inactive form in association with KEAP1 [21]. Until recently, *NFE2L2* was not considered an oncogene; rather it was thought to either facilitate or impede tumorigenesis depending on when during tumor evolution its deregulation occurred [22]. When deregulated early, its down- stream target genes were believed to suppress reactive oxygen species (ROS), reduce oxidative damage and limit the accumulation of new mutations, thereby slowing the emergence of more aggressive clones and serving as a *de facto* tumor suppressor. In contrast, NFE2L2 activation at later times might allow already activated oncogenes such as Myc and Ras that are known to produce toxic ROS, to be expressed at higher levels without causing further stress and toxicity, thus permitting higher rates of proliferation [17,23].

Less Common Oncogenic Drivers

The above-described factors and pathways represent those that are the most commonly deregulated in human HB and thus contribute most heavily to the altered mutational landscape. However, other HB drivers have been described, including somatically acquired ones in the *TERT, APC, AXI1* and *AXIN2*, genes [16,24-27]. Interestingly the latter 3 encode components of the APC complex and mutations in them are thus functionally equivalent to mutations in the *APC* and *CTNNB1* genes.

Mouse Models of Hepatoblastoma

Several mouse models of HB have been developed although only one of them can actually recapitulate different human HB molecular subtypes [19,28]. The model is simple, highly efficient and sufficiently versatile in that it can be used to express various combinations of drivers and their modifiers with highly reproducible outcomes. It also allows the ability to assess not only whether the factors of interest are directly causative but also whether tumors expressing different combinations of oncogenes vary in their appearances and/or behaviors. The first report of this model by Tao, et al. utilized the method of Hydrodynamic Tail Vein Injection (HDTVI) to deliver Sleeping Beauty (SB) vectors encoding a patient-derived mutant form of β-catenin (△90) and a constitutively active form of YAP (Y^{S127A}) [19]. Interestingly, the HDTVI of △90 or Y^{S127A} alone did not generate tumors, indicating that at least 2 cooperating hits were necessary to drive tumorigenesis in vivo. These findings were soon followed by our own demonstration that patient-derived missense mutations of NFE2L2 (L30P and R34P), which were also non-oncogenic when expressed individually, each generated HBs in collaboration with either Δ90 or Y^{S127A} [22]. Moreover, the combined expression of all 3 factors generated highly aggressive tumors [22]. Each of the 4 possible tumor groups, which we have termed B+Y, B+N, N+Y and B+Y+N could be distinguished based on various combinations of growth rates, histology, biochemical properties, and transcriptional profiles [22]. Moreover, the studies established for the first time the direct role of NFE2L2 in oncogenesis.

Recently Resolved Questions

Until recently, the molecular simplicity of HB appeared incapable of explaining why some patient tumors grow faster than others, why some present with multifocal or metastatic disease and how multiple histologic subtypes originate. Moreover, it could not account for the 50% or more of human HBs that failed to localize both β-catenin and YAP to the nucleus [17,19]. The utility of the above-described mouse model [19] was affirmed by the fact that it simultaneously provided answers to all these questions by showing that different combinations of β-catenin, YAP^{S127A} and NFE2L2 mutants could generate HBs with different features [22]. Subsequent work showed that different patient-derived β-catenin mutants further contributed to the diversity of HBs [18]. This was attributed to variations in the levels at which the mutants were expressed, were able to escape their retention by APC and obtain entry into the nucleus and were able to activate different target genes [18].

Unresolved Issues

Despite the long-standing questions mentioned above having been resolved, at least 3 important ones remain. These have not been adequately addressed due to the lack of sufficient numbers of patients and inconsistent molecular profiling of HBs. Despite these impediments, they are of significant clinical relevance and deserving of attention.

Is the "One Size Fits all" Approach to Chemotherapy Really Optimal for all Patients?

Much work has shown that chemotherapeutic responses (or lack thereof) in cancers that superficially appear otherwise iden-

tical are often dictated by their underlying molecular drivers and transcriptional profiles [29,30]. Such findings have largely motivated the ongoing expansion of therapy regimen individualization that is designed to reflect these differences. The means by which treatments can be personalized can range from altering the dose or duration of one or more drugs to adding new ones that are specifically designed to target particular mutant oncoproteins such as Bcr-Abl or B-Raf^{V600E} or particular gene rearrangements such as those involving *MLL* in the infant form acute lymphocytic leukemia, which has a much worse prognosis than the more standard type that occurs in older children [31-33]. HB chemotherapeutic regimens, designed to cure or to shrink primary tumors in order to facilitate their subsequent surgical removal, are currently not individualized as they are for the cancers mentioned above. Rather, each patient is generally treated with a "one size fits all" regimen without regard as to whether and how the underlying molecular drivers might influence the response [6]. Thus, given the frequencies with which different combinations of altered b-catenin, YAP and NFE2L2 signaling are involved in the pathogenesis of HB, it is important to ask whether all HBs should be treated in the same manner. A corollary to this question is whether the 20-30% of HBs that recur after therapy represent a particular molecular subset that was already inherently more resistant to the standard drugs prior to the initiation of therapy and that was able to acquire resistance more rapidly or efficiently.

Does Drug Resistance Develop in the Same Way Among Different Tumors?

As many of 30% of HBs recur following standard treatments [6,34,35]. These are uniformly chemo-resistant with the only therapeutic option now being OLT [9]. A small number of recent studies have identified sufficient genetic heterogeneity among recurrent HBs to suggest that the acquisition of chemo-resistance may be dependent upon the underlying genetic landscape [36,37]. Collectively, these findings raise at least 2 additional important questions. First, do different subtypes comprise this chemo-resistant cohort and second, are the mechanisms underlying the acquisition of chemo-resistance similar among the different subtypes?

Can Chemotherapeutic Responses for Individual Patients be Predicted?

Knowing that HBs belonging to different molecular categories possessed differential responses to standard chemotherapeutic regimens could potentially allow chemotherapeutic regimens to be individualized and optimized. Understanding the pathways by which such tumors escape successful treatment and develop resistance and whether they differ among different molecular subtypes, might also provide insights into how resistance could be avoided or circumvented.

The Pressing Need for HB Cell Lines

Very few established HB cell lines exist and only one of these, HepG2, is available from the ATCC. This ready accessibility and its nearly 45-year history have contributed to it being the most commonly used HB cell line. However, how representative these cells are of HB is highly questionable for at least 3 reasons. First is its having been derived from the tumor of a 15-year-old boy whose age alone placed him well outside the typical range for HB [38-40]. Second, despite having been well-characterized and leaving little doubt that they bear the characteristics of HB and not hepatocellular carcinoma with which they were once confused, HepG2 cells bear none of the mutations most associated with HB (i.e. β-catenin, NFE2L2, TERT, APC, AXIN1) [40,41]. Third, HepG2 and several other HB cell lines have been maintained in vitro for many years during which time they have been subject to repeated sub-cloning, and genetic drift. Another problem with the currently limited number of HB cell lines is that, collectively, they are not fully representative of the Wnt/β-catenin, Hippo and NFE2L2 pathway alterations that characterize the majority of HBs discussed above [17]. Regardless of the number of cell lines that exist, either currently or in the future, it will also never be easy to determine the degree to which different tumor behaviors, particularly drug responses, are the result of different combinations of oncogenic drivers or germ-line genetic differences among the individual from which the tumor lines are derived.

How do We Get There?

Determining how chemotherapeutic drug responses and the development of resistance by individual HBs are influenced by different combinations of oncogenic drivers requires immortalized cell lines that can be generated easily and rapidly from actual tumors. Ideally, these would express the most common combinations of oncogenic drivers but would be otherwise isogenic. This latter trait is particularly important as it would equalize the individual genetic differences that are unrelated to the drivers and that cannot be avoided when dealing with human tumors. All of these issues can be addressed through the use of HBs generated by the mouse model described above.

Despite the ease with which the tumors described above can be generated, the major problem facing the generation of cell lines remains the overall refractoriness of the tumor cells to *in vivo* immortalization. Indeed, we have repeatedly been unable to establish cell lines from any of these tumors in standard tissue culture medium. Incubating minced fragments of HBs does lead to the release of their cellular contents, which attach to the surface of tissue culture plates where they are able to survive for several weeks. However, they remain in a quiescent state. HBs generated by the combination of β-catenin (△90) +YAP^{S127A} show variable down-regulation of the p19^{ARF} tumor suppressor, whose role in cell immortalization and tumorigenesis is well-documented [42,43]. Speculating that a more complete p19^{ARF} loss would predispose to HB immortalization in vitro, we generated tumors in which the *Cdkn2a* locus, which encodes p19^{ARF}, was inactivated by Crspr/Cas9 targeting. By this method, we have thus far established nearly a dozen such cell lines in as many attempts and are currently doing so with HBs driven by all 4 combinations of oncogenic drivers. In addition to permitting the drug sensitivity/resistance studies discussed above, these cell lines should be useful for a number of other studies. These include experiments in which the extracellular environment must be

maintained and/or changed under scrupulously controlled conditions and those designed to identify novel and/or driver-dependent sensitivities using Crspr-based genome-wide screens. Preliminary findings that these cell lines are readily transfectable indicates that they will also be easy to modify genetically in order to perform Crispr screens and to test the consequences of altering the expression of the genes that are identified by these methods.

Shortcomings

The availability of isogenic immortalized HB cell lines, driven by defined combinations of oncogenes and/or tumor suppressors should permit experiments that have previously been impossible to perform *in vivo*, while also accelerating those that, while feasible *in vivo*, were difficult, expensive or time-consuming. However, as with all such cell lines, these will necessarily be associated with several general as well as specific caveats. In the first case, any findings obtained will require *in vivo* confirmation in order to ensure that the results are simply not the result of *in vitro* adaptations of the cell lines. It may also be necessary to reconcile the fact that, whereas the loss of expression of $p19^{ARF}$ is variable in both mouse and human primary HBs (unpublished findings and ref. 43) the cell lines we are deriving are deliberately selected so as to express no $p19^{ARF}$.

Conclusions

The rarity of HB and HB cell lines, previous failures to adequately characterize tumors molecularly, difficulties in generating immortalized cell lines from tumors and the impossibility of studying human tumor cell lines in isogenic backgrounds has limited our ability to utilize the few cell lines that are available in more productive ways. In contrast, the ability to readily establish immortalized cell lines from primary isogenic murine tumors with defined driver mutations of one's choosing would solve many of the problems that currently confront the HB research community. In addition to allowing for the rapid comparative testing of drug sensitivities among various cell lines and the identification of new effective agents, the controlled establishment of drug-resistant cell lines would allow the examination of these resistant phenotypes at various stages during their evolution. Such lines could prove useful in providing insights into the pathways taken by these cells during the acquisition of increasingly high- level resistance. Both drug-naive and drug-resistant cell lines would also be used to perform genome-wide and unbiased Crispr-based screens that would identify genetic susceptibilities and inform us as to how new drugs could be designed and resistance to old drugs could be overcome or circumvented.

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Conflicts of Interest

None.

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