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Commentary

# Retinoblastoma Progression

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The importance of our world's constant change was famously recognized by Heraclitus of Ephesus (535 BC–475 BC), who is quoted as saying that because of such change one cannot step into the same river twice (Plato). Heraclitus' disciple, Cratylus, supposedly one-upped his master by noting that because of the constant flow, one cannot step into the same river even once! Today, these views can inform our understanding of cancer, a disease that continuously changes as it selects for increasingly proliferative cells. From Heraclitus' standpoint, evaluating a cancer may be akin to entering a fast moving and constantly evolving current. However, despite this recognition, it can be difficult to grasp how cancers change, and especially whether they change in predictable or in unpredictable ways. In this issue of *EBioMedicine*, Josephine Dorsman and colleagues show that it is possible to use gene expression profiling to outline the channels through which certain cancers reproducibly flow (Kooi et al., 2015).

Kooi, Mol et al. focused on the childhood retinal cancer retinoblastoma, which is usually initiated by biallelic inactivation of *RB1*. The authors first used hierarchical clustering of gene expression profiles to determine if retinoblastomas comprise a single "type," as proposed by one group (McEvoy et al., 2011), or comprise distinct subtypes, as suggested by another (Kapatai et al., 2013). Unsatisfyingly, they found that retinoblastomas either could be divided into two groups *or* could form a continuum of phenotypes, depending upon which clustering algorithm was used. However, using the algorithm that yielded two groups, they found that the genes distinguishing the groups varied continuously rather than dichotomously across all retinoblastoma samples, implying that their division into groups was artificial. One end of the tumor spectrum had a strong photoreceptor signature, whereas the other end had M-phase and mRNA and ribosome synthesis (RNA biogenesis) signatures, and these signatures varied inversely as well as continuously across the spectrum. Moreover, tumors with higher "photoreceptorness" had smaller size, younger age at diagnosis, increased histologic differentiation, and fewer somatic DNA copy number alterations (SCNAs), compared to those with higher M phase and RNA biogenesis phenotypes. The findings indicate that retinoblastomas progress from smaller, more differentiated, and more genomically intact tumors towards larger, less differentiated and more genomically altered tumors likely having greater proliferative potential.

One implication of this progression model is that $RB1^{-/-}$ retinoblastomas are likely to have a single cell of origin, rather than different origins for the now unlikely different subtypes. Notably, Kooi, Mol et al. found that differentiated tumors highly expressed cone-specific but not rod-specific genes, consistent with a proposed cone precursor origin followed by dedifferentiation (Xu et al., 2014). The findings are also consistent with a model in which the earliest $RB1^{-/-}$ lesions are self-limited (as well as cone-like (Xu et al., 2009)) retinomas that subsequently convert to retinoblastoma and acquire SCNAs (Dimaras et al., 2008). Importantly, the lack of SCNAs in the most differentiated tumors (Kooi et al., 2015) confirms prior evidence that recurrent SCNAs are not needed for retinoblastoma development (Zhang et al., 2012). Thus, the basis for the conversion of retinoma to differentiated retinoblastoma remains unclear.

Kooi, Mol et al. also shed light on the rare retinoblastomas driven by *MYCN* amplification ($MYCN^{A}$) rather than by *RB1* loss (Rushlow et al., 2013). Although $MYCN^{A}$,$RB1^{+/+}$ tumors have distinct histology, earlier onset, and possibly more aggressive behavior (Rushlow et al., 2013), the two examples in the Kooi, Mol et al. cohort fell within the photoreceptorness and M phase and RNA biogenesis signature spectrum of $RB1^{-/-}$ tumors. However, they also differentially expressed many cell cycle and other genes, bringing into question whether they have a distinct cell of origin or have the same origin but are phenotypically modulated by their *MYCN* amplification and retained pRB.

Finally, the study has interesting clinical implications. Surprisingly, differentiation status did not correlate with optic nerve or choroidal invasion, nor with retinoblastoma stage, implying that cellular evolution does not underlie current clinical progression metrics. Moreover, upon explant, the less differentiated tumors were on average more sensitive to several chemotherapeutic agents. While the high variability of the drug responses and limitations of *ex vivo* culture preclude direct clinical translation, the recognition that drug sensitivity evolves in a predictable manner is a first step towards targeting the distinct cellular entities.

While Kooi, Mol et al. make a strong case for retinoblastoma progression, mechanistic questions remain. For example, it is unclear whether most of the early retinoblastoma cells gradually dedifferentiate or if only rare cells dedifferentiate and then gradually overgrow their counterparts. It is also unproven whether specific SCNAs mediate the decreased photoreceptorness and increased M-phase and RNA biogenesis-related gene expression. The mechanism underlying these gene expression

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changes is of great interest since similar changes may contribute to progression of other malignancies.

While the current findings clearly change our understanding of retinoblastoma, cancer researchers have stepped into similar rivers before. In the 1980s, it was recognized that progression of colorectal cancer from early adenoma to carcinoma and metastatic disease was accompanied by specific genetic changes (Fearon and Vogelstein, 1990), and similar progression has been noted in many other malignancies. But the Dorsman group's study is unusual in that progression states were discerned primarily through gene expression profiling rather than through histopathological criteria, and they portend an era when targeted therapies may be tailored to attack the predictable cellular states through which cancers evolve. The lesson is that cancers can progress in predictable ways. We must embrace this lesson and use it to our advantage.

## Conflict of interest

The author declares no conflicts of interest.

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