As cancer is a multifactorial disease, the use of and data mining derived from integrated genome and epigenome studies coupled with biochemical, biological, molecular, and epidemiological data is vital to its understanding (Nebbioso et al., 2018). Although available therapies lead to regression or improve control of a wide variety of tumors, some do not respond to therapeutic patterns, displaying low survival and high frequency of recurrence. Highly lethal tumors are a group of cancers with (i) an average 5-year survival rate of about 20% (or less), commonly characterized by frequent late diagnosis (associated with the onset of advanced disease symptoms), and (ii) biological aggressiveness and limited treatment efficacy. Early biomarkers of response and novel therapeutic approaches for these tumor subtypes represent an unmet need. Alternative treatment options include so-called “targeted therapies”, which inhibit pro-tumorigenic pathways frequently altered by somatic mutations. Although these therapies are largely efficacious, they are challenged by the development of resistance.

Targeting transcriptional dependencies associated with deregulation of chromatin regulators, transcription factors, and/or cofactors may therefore provide a different strategy (Bradner et al., 2017). Inhibition of bromodomain and extraterminal domain (BET) proteins (French, 2016) is emerging as a promising anticancer strategy to block transcriptional dependencies, yet resistance development remains a challenge (Kurimchak et al., 2016). Uveal melanoma (UM) is the most common primary intraocular malignancy in adults in the United States, in which roughly 50% of patients develop metastases, predominantly to the liver. Since no therapies have been approved for metastatic UM (UMM), prognosis is very poor, partially as a result of development of resistance to targeted therapies. BET inhibitors (such as PLX51107) are currently being tested in clinical trials for patients with advanced malignancies including UM and UMM, but resistance has been reported.

The present study by Chua et al (2019) suggests that inhibition of the FGF receptor (FGFR) pathway improves the response of UMM to BET inhibitors. Specifically, they found that FGFR2, but not other growth factors, provides resistance to growth suppression by BET inhibitors in UMM cells as well as in vivo. FGFR2 effects were reversible by FGFR inhibitors. BET inhibitors also increased FGFR protein expression in UM cells and in patient samples. Interestingly, PLX51107 increased in vivo tumor growth of UM cells co-injected into mice with hematopoietic stem cells, and the combination of PLX51107 and the FGFR inhibitor AZD4547 suppressed tumor growth. Thus, the authors suggest that in patients with UMM, co-targeting of the FGFR2/FGFR cascade is required to improve the efficacy of BET inhibitors, preventing the development of resistance. The finding that liver cells secrete FGFR2, crucial to conferring resistance (schematically summarized in Fig 1), is of particular interest, since it provides an example of how to delineate the interaction of organ-specific cells of the liver with tumor cells. It may indicate that liver microenvironment plays an active role in reducing the efficacy of BET inhibitors, and co-inhibition of FGFRs by AZD4547 treatment significantly suppresses tumor growth compared to PLX51107-treated mice.

Research approaches of this kind may also be of great importance for future therapies against hepatic metastatic disease. The fact that different mechanism(s) of resistance to BET inhibitors have been reported points to the development of cancer-specific, and possibly patient-selective, tumor microenvironment targeting as well as potential specific organ-context features. This strongly suggests that therapeutic regimens designed to overcome cancer resistance might not only work directly against cancer cells, but likely reset the homeostatic control of cancer development in the whole body. This opens the way toward even more complex personalization in which, depending on the clinical and systemic case, resistance mechanisms might be highly heterogeneous. Intriguingly, different cancer types may share some of these deregulations, suggesting that very diverse cancers might display a common denominator for resistance development. As also described by Chua et al (2019), resistance to BET inhibitors in ovarian cancer was associated with elevated expression of FGFRs (Kurimchak et al., 2016). The mechanisms underlying BET inhibitor-induced overexpression of FGFRs are unclear, but may involve modulation of BRD4-induced regulation of FGFR transcription. BRD4 occupancy was shown at the promoter region of receptor tyrosine kinases and was attenuated by BET inhibitors (Stuhlmiller et al., 2016). Thus, although different mechanism(s) for FGFRs are reported, a therapeutic scheme combining BET inhibitors and FGFR inhibition by AZD4547 treatment may be beneficial also against ovarian cancer.
Metastatic uveal melanoma (UMM)

Resistance to BET inhibitors

Hepatic stellate cells

\[ \text{FGFR} \]

\[ \text{Tumor cells} \]

\[ \text{FGFR} \]

\[ \text{BET inhibitors} \]

\[ \text{FGF2} \]

Sensitization to BET inhibitors

Hepatic stellate cells

\[ \text{FGFR} \]

\[ \text{Tumor cells} \]

\[ \text{FGFR} \]

\[ \text{FGFR inhibitors} + \text{BET inhibitors} \]

\[ \text{FGF2} \]

\[ \text{TUMOR GROWTH INHIBITION} \]

\[ \text{TUMOR RESISTANCE} \]

\[ \text{BET inhibitors} \]

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**Figure 1.** Mechanism of resistance to BET inhibitors in UMM: FGF2 (red) increased production (LSC, yellow) and tumor (black) FGFR-increased expression leads to BETi resistance (left). Combination treatment BETi+FGFRi suppresses tumor growth (right).

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