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“Positions, please!”

For over a decade, a class of drugs called BET inhibitors has been tested in cancer trials with high expectations. The biology looked promising. Many cancers depend on oncogenes that “Bromo- and Extra-Terminal domain” (BET) proteins help activate, so blocking BET proteins should slow tumor growth. In the lab, it often did. In patients, results were mostly disappointing: limited responses, significant side effects, and no clear way to predict which tumors would respond at all. A new study from the Max Planck Institute of Immunobiology and Epigenetics (MPI-IE) in Freiburg now offers a possible explanation for why, and points towards developing a more precise mode of therapy.

To the point:

- **Why cancer drugs often disappoint:** A study by the Max Planck Institute of Immunobiology and Epigenetics shows why so-called BET inhibitors have frequently been less effective than expected in clinical trials.
- **Two similar proteins, two different roles:** The researchers demonstrated that the BET proteins BRD2 and BRD4 perform distinct functions during gene activation—an important difference that influences how these drugs work.
- **Implications for cancer therapies:** Most current BET inhibitors block both BRD2 and BRD4. The new findings suggest that distinguishing more precisely between their functions could lead to more targeted and potentially more effective cancer treatments.

Treating an entire protein family as single target

BET inhibitors were developed to block a shared domain that all BET proteins use to bind chromatin, the tightly packed complex of DNA and proteins in which genes are stored and regulated. Blocking chromatin binding seemed a reasonable strategy to silence the machinery that reads the oncogenes, hinging on the assumption that all BET proteins do roughly the same thing.
A new study by the lab of Asifa Akhtar offers a more nuanced picture. Their work reveals that two key BET proteins from the family, BRD2 and BRD4, perform distinct roles at different stages in gene activation. BDR4 drives the step that most current therapies target: releasing RNA Polymerase II, the enzyme that pushes genes into active transcription. But BRD2 acts earlier at an initiation stage, recruiting and organizing the molecular machinery that gets transcription started in the first place.

A molecular stage manager

Blocking both BRD2 and BRD4 simultaneously, as current inhibitors often do, disrupts two different steps of the same process at once and produces effects that are difficult to predict and highly context-dependent. “Think of gene activation like stage production. BRD2 sets up the stage: assembling the props, costumes and actors to ensure preparations run smoothly. BRD2 then gives BRD4, the actor, the “start” signal to begin with the performance,” says Asifa Akhtar, who led the study at the MPI-IE. “Previous studies had been focused almost entirely on the performance. Our data shows that the setup work happening before is just as critical for gene activation,” explains Asifa Akhtar.

BRD2 had long been considered the less interesting of the two proteins. The new study suggests the opposite may be true. Part of what makes BRD2 distinctive is what it responds to. The enzyme MOF places specific chemical tags known as histone acetylations on chromatin. These bookmarks act as a sophisticated labeling system to control which genes are read on the DNA and tell BRD2 where it needs to start its work. BRD2 is uniquely sensitive to these »bookmarks«: remove MOF, and BRD2 loses its grip on chromatin, while other BET proteins are largely unaffected. “The findings support a model in which acetylated chromatin creates a platform that allows regulatory proteins like BRD2 to concentrate and prepare the transcription machinery for when it will be needed,” says first author Umut Erdogdu from the Akhtar lab.

The power of clustering

Beyond this specificity, BRD2 actively organizes the transcription machinery at the spatial level, forming dynamic clusters at

gene binding sites that concentrate the necessary molecular components precisely where transcription needs to begin. “To understand the importance of the clustering for gene transcription, we removed only the specific part of BRD2 responsible for forming clusters while leaving the rest of the protein intact,” explains Umut Erdogdu.

The result was striking: even though BRD2 was still present in the cell nucleus, transcription stalled almost as completely as if the entire protein had been deleted. “This demonstrates that clustering is not a side effect, but a functional feature of transcription regulation. And like a stage manager, BRD2 ensures that every performer and every piece of equipment is in place before the curtain rises,” says Asifa Akhtar.

The findings reframe what selective and more nuanced BET inhibition could look like in the future. Rather than designing drugs that block the shared chromatin-reading domain across all family members, a promising goal could be to distinguish between the distinct roles of BRD2 and BRD4 during gene activation. Understanding these differences could be a step towards therapies that are more targeted and easier to predict.

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