

Yao Xiang CBX3, IFN γ and Why Thinking Twice Matters

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CBX3 antagonizes IFN γ /STAT1/PD-L1 axis to modulate colon inflammation and CRC chemosensitivity. Xiang *et al.*, EMBO Molecular Medicine, June 2024.

<https://doi.org/10.1038/s44321-024-00066-6>

Keywords: CBX3 (HP1 γ); IFN γ Signaling; Colon; Inflammatory/Immune Response; Colorectal Cancer

Problem - IFN γ is crucial for gut homeostasis and its dysregulation is linked to diverse colon pathologies, such as colitis and colorectal cancer (CRC). Given the important role of IFN γ /STAT1/PD-L1 axis in innate and adaptive immune responses, targeting the IFN γ signaling pathway could improve treatment efficacy for UC or CRC treatment.

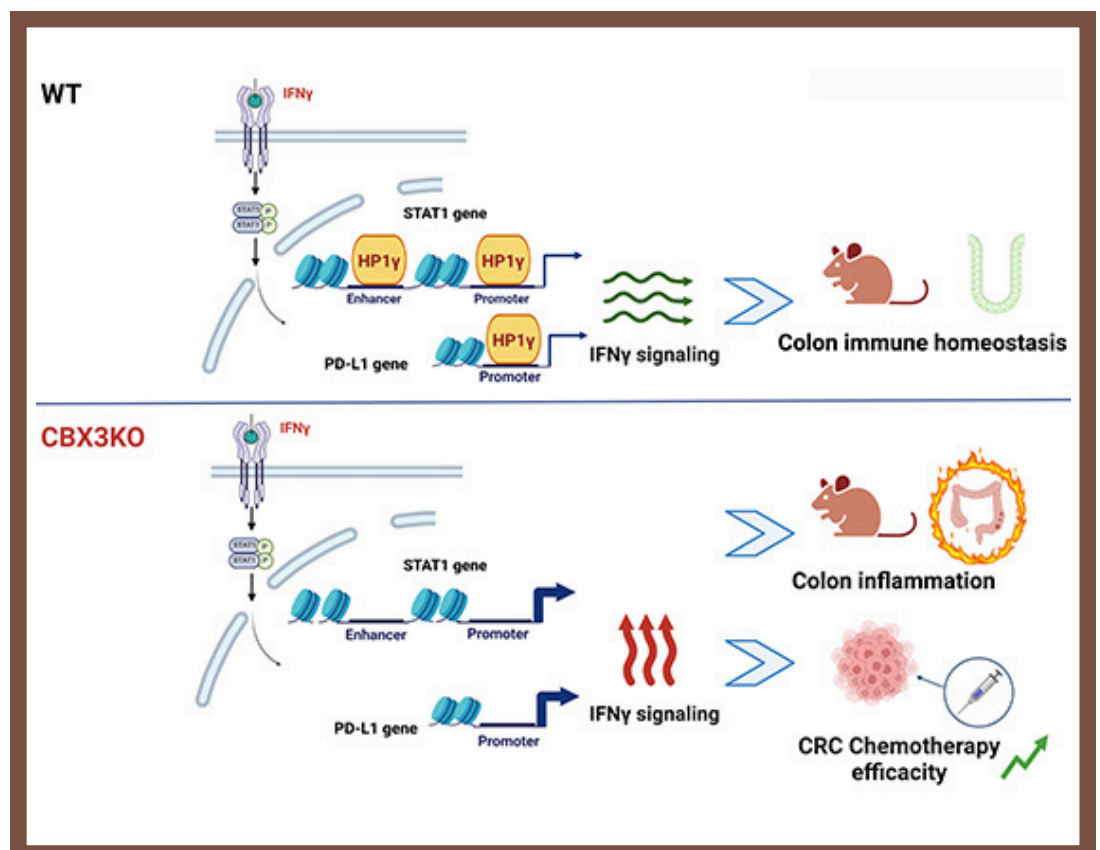
Results - CBX3 was identified as an antagonist of the IFN γ signaling cascade in the colon epithelium via repression of STAT1 and CD274 transcription. Upon IFN γ stimulation, CBX3 binding to STAT1 and CD274 promoters was decreased, concomitant with their increased gene expression. CBX3 depletion led to a strong increase of STAT1 and PD-L1 expression under IFN γ stimulation, suggesting a role for CBX3 in the control of IFN γ -stimulated immune gene activation. Accordingly, CBX3 deletion resulted in chronic mouse colon inflammation, accompanied by upregulated STAT1 and CD274 expression. In particular, CBX3 deletion heightened CRC cells' sensitivity to IFN γ , which ultimately enhanced their chemosensitivity both in vitro and in vivo.

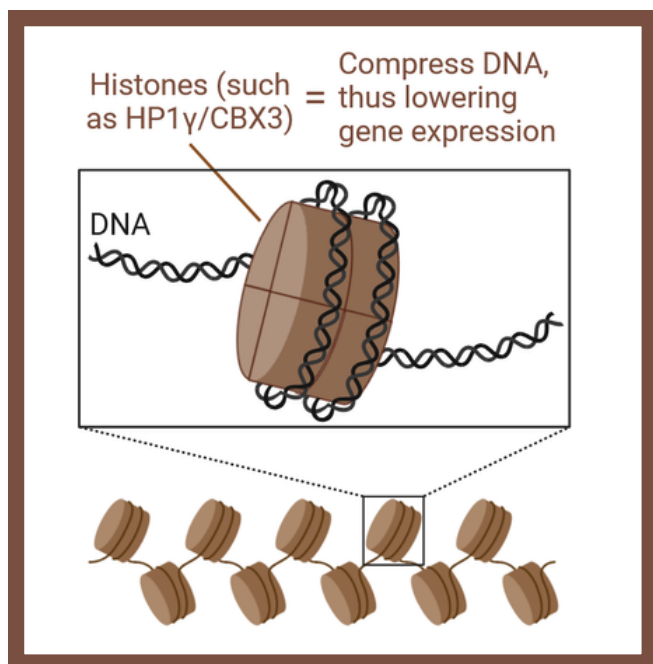
Impact - Our work identifies an interplay between CBX3 and IFN γ signaling that leads to regulation of the immune response in colon epithelium and of chemo-resistance of colorectal cancer. CBX3 appears as a potential target to enhance IFN γ -related therapeutic efficacy in UC and in colorectal cancer.

Graphical Abstract:

In a few words,
what's the take-
away message from
your paper?

The main point we addressed in this paper is that HP1 γ (or CBX3, a histone-like protein) is an antagonist of IFN γ signaling. And when we knocked out (KO) CBX3, we found that colorectal cancer is more sensitized to IFN γ stimulation, which is a benefit for chemotherapy.





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How long did the work for this paper take?

2 years. We finished the *in vitro* and *ex vivo* experiments almost during the first year of my PhD. We tried to submit [but] every reviewer told us we need to do *in vivo* experiments so that we could validate our conclusions [and] we convinced the PI to do *in vivo* experiments. So the total time for the experiment stuff is I think less than two years.

It took one year from the first rejection until the acceptance of the paper in the end?

Yeah, at the beginning we sent it in 2023, and at the beginning we submitted it in this journal actually and they rejected it. We didn't receive totally negative comments because the reviewer said our work is interesting, but we just lack *in vivo* experiments and the reason why they didn't give us some chance to improve at that moment is because of the journal's schedule. At that point because we didn't have *in vivo* experiment and it was really complicated to finish on time, they said: this time we will reject, but if you do the *in vivo* experiments, you can try again and we will consider as a new manuscript. But during this period, we also tried other journals. [...] We just organised figures and put new formats, we didn't add new data. But in the end, me and my supervisor talked about this and I think this journal is a very good journal that really matches our topic. And the 3 reviewers we had gave us really good advice. So we were thinking that we should follow their suggestions and do more experiments so that we could come back to send it again.

You have another paper in the works, is this work Part 1 of your thesis?

Yep, during my thesis, this is Part 1. I also did some work for a previous postdoc for his Nature Communications paper, and I am the 2nd author. In addition, I have another project which is about the role of CBX3 in ferroptosis.

That second paper, is it the continuation of this story, or a completely different one?

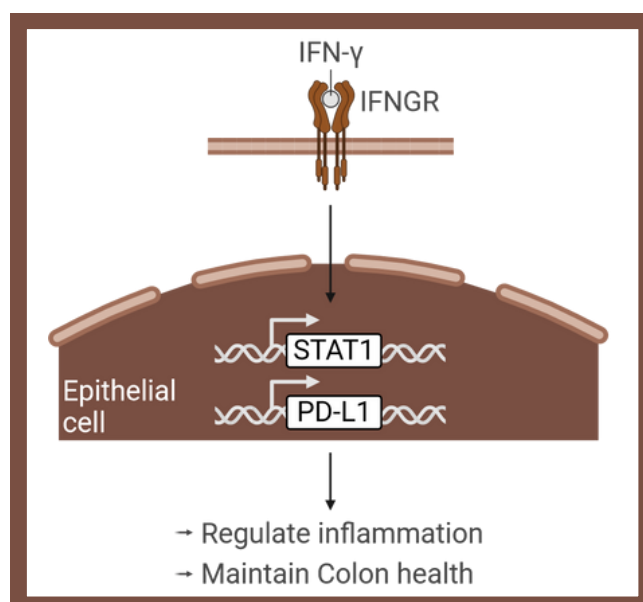
It's a little bit different, but for sure it's linked with this project as well because in this paper we found that CBX3 antagonizes IFN γ . IFN γ is reported to be involved in ferroptosis. There is a Cell paper that was published a few years ago that reported that IFN γ can induce ferroptosis and inhibit one key factor in the antioxidant system called SLCA711. So we hypothesize that CBX3 would inhibit ferroptosis through antagonizing IFN γ .

How much of this paper between the idea, the story, the experiments, the methods was your personal input?

I think both of me and my PI. Basically, every step, idea and results I get, we discuss it with my supervisor and we have an appointment to decide what to do. [Regarding techniques], for organoids we had the protocol for the small intestine. It was a previous postdoc that did this and he gave me the protocol and so I just followed the protocol and tried it!

Did you have a Eurêka moment? Like an "Oh wow, I found something amazing!" moment during your thesis?

I would say there is not only one moment. First, at the beginning we did the *in vitro* model we use SW480 cell lines and [our very impressive] results quite encouraged us, but you know cell lines have different backgrounds and a lot of things could change [...] so we used another cell line called HT29 and did the knockout and did the same experiment and it was even better. That was really a very happy moment and quite verified our hypothesis. The second moment was the *ex vivo* model, [...] when I got the result, it was perfect; it matched with our *in vitro*. And the third moment I would say is also the last part of the paper, for the chemotherapy part, a very basic and easy experiment called MTT assay. We used 5-FU which is a very common medicine used to handle cancer, and it just gave us very amazing data, it was driving us to go *in vivo*.



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And how do you feel about your paper now?

I think we've got quite a good start, but in this topic we still have huge things that we can go deep into, which is quite a pity because I'm going to leave! I think what makes me very happy is also that from this work during my thesis, we really opened a lot of windows for the future work [...] like my second project.

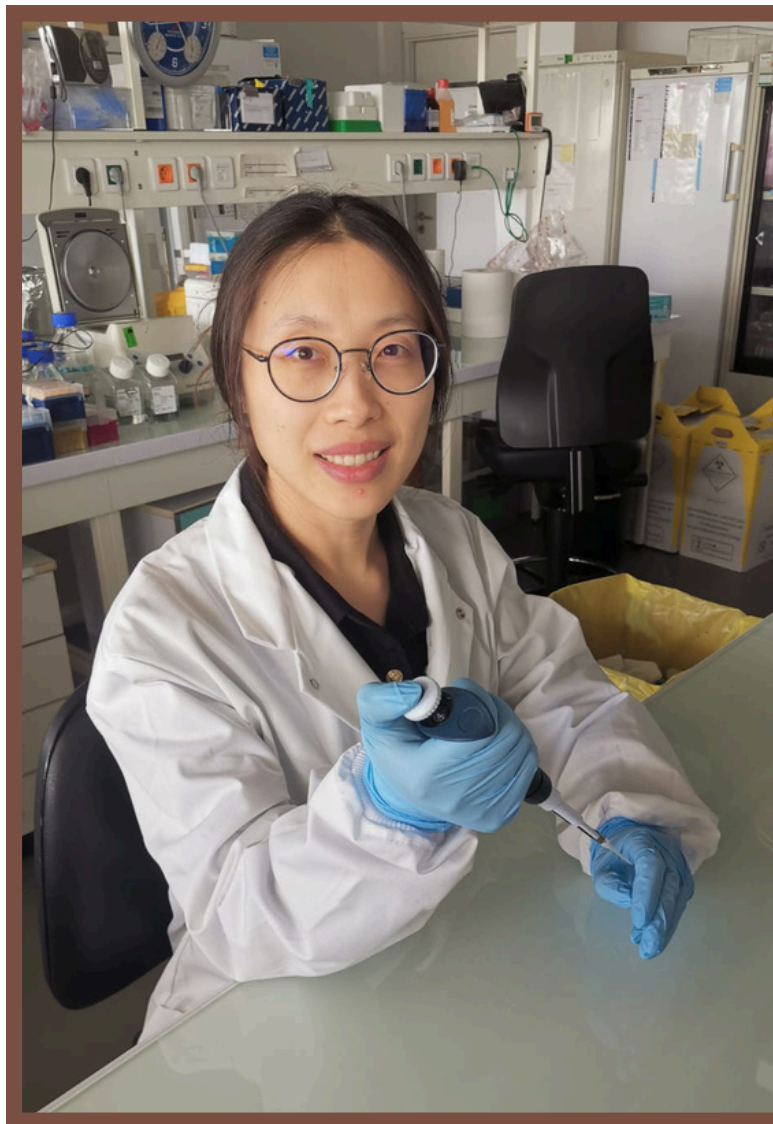
More about Yao's journey

Do you already know what you're going to do after your PhD?

For sure I'm quite interested in science, like to do projects, to do research. So I'm thinking of finding a postdoc. But right now, I don't really spend a lot of time on it because I'm writing my thesis and because of the time limitation... And the topic, I'm quite interested in immunology and I would really like to work in something that has the possibility to go to industry. [...] From my PhD journey, I also want to find a lab where I can have funding and really do whatever I want.

What drove you to do a PhD in the first place?

I think it starts from the bachelor. My bachelor degree is canonical medicine, so generally students don't need to do [research] projects because we go to the hospital to do an internship. [...] But I participated in a project called "College Students' Technological Innovation" during that time and we have one publication. It was the first time I did experiments with mice. I found something I'm good at and also I'm interested in! In the lab or in the animal facility, I could almost forget about time.



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“If a person is too focused [...] they are inside their box... they can't go further.”

How would you qualify your work/life balance?

I think for most of us Chinese students, we don't have this problem because we were basically working at least 10 hours in master's and we didn't have a lot of holidays [...], maybe 10 days a year, and even during the weekend we work. So for us, this is heaven. [But] you can't really let your life only have science. You need to have your own friendship circle. You need to do other things. I think other things also somehow help you continue your research. If a person is too focused, and doesn't have time to take a break, to jump out, they are inside their box... they can't go further.

Do the skills you learnt during your thesis help you feel prepared for postdoc?

[One thing] I learned was to be prepared before starting every experiment, and to think twice before doing an experiment because if you mess it up, it takes more time and you spend reagents, antibodies, etc, and gain nothing. So it's always better to think twice before you're doing an experiment and try to make every step or experiment correct so you spend less time and work more efficiently. [...] During this thesis, I learned how to solve problems by myself and I learned how to build a project, do the right plan, and to make things work. So from this point, I'm prepared.

“It’s always better to think twice before you’re doing an experiment and try to make every step correct.”

Some advice for 1st year PhD students or applicants?

[During an experiment], take care of the key steps and relax on maybe less important steps, so that you can do it easily. Because you can't spend 8 hours focused on something, but if you do good in the key steps, you will do good overall.

[Regarding your research], collect every information, compare and think about the knowledge. Compare every [experiment] and see the difference between them and figure out what's the logic inside. Understand the science behind your techniques and know when to put your focus in the experiments. Keep critical thinking. Research is research. You have a hypothesis but things could not follow what you expected. Then you need to trust your results and maybe find another hypothesis.

[For the Chinese students]: I think it's quite complicated for us because our education system is totally different and we don't have a lot of chances and opportunities from abroad. So the first suggestion is to just open your mind and be confident. I think because of the language problem, most of us are not comfortable at the beginning. But just trust yourself and think that you could do good. Open your mind, open your eyes to find out about more chances, and don't limit yourself!

**“Keep critical thinking. Research is research.
[...] Trust your results.”**

The interview was conducted in July 2024.

Yao is currently looking for a postdoc, feel free to share this interview or contact her!

Dr. Yao Xiang - xiangyao.ecole@outlook.com

Scientific Highlights - April 2025

Who are we?

We are PhD students from the BioSPC doctoral school and representatives of BioSPC students. We dedicate time and energy to make the PhD journey more pleasant for the most of us and to meet new people who share common interests.

What is this project?

The SciHighlights project comes from the will to highlight the achievements of BioSPC PhD students, make accessible all scientific fields across the doctoral school and share the behind-the-scenes of a thesis path or a publication.

Credits

Interview: Laetitia Camard & Audrey Laurent
Transcript: Ahmad Maswadeh
Editing: Audrey Laurent
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Have an achievement to highlight?

