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Short Commentary

Commentary Referring to Pericyte FAK Negatively Regulates Gas6/Axl Signalling To Suppress Tumour Angiogenesis and Tumour Growth

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The published research article utilized multiple mouse models including melanoma, lung carcinoma and pancreatic B-cell insulinoma. Two hallmarks of cancer [1] such as angiogenesis and tumour growth had been evaluated. Two major molecules FAK (focal adhesion kinase 1) and Axl undertook the innovative roles of this elegant paper. They both belong to protein Tyrosine Kinase (TK) family [2]. TKs gained mounting attention not only due to their higher expression in many cancer types but they also can be targeted by small molecule inhibitors or peptides as effective drug targets over the past decades [3]. FAK and Axl were two negatively expressed molecules. Ligand Gas 6 and receptor Axl consisted of receptor TK signalling pathway mediating the tumour igenesis [4].

➢ **Results section dissected as five parts**

- Pericyte FAK deficiency increases tumour growth and tumour angiogenesis.
- Determining the molecular players in the enhanced tumour angiogenesis in pdgfrβcre+; fakfl/fl mice.
- Exogenous Gas6 enhances angiogenic responses via pericyte Axl in FAK^{KO} pericytes.
- Exogenous Gas6 stimulates angiogenesis by elevating Cyr61 in FAK^{KO} pericytes.
- Reduced expression of pericyte FAK is associated with human melanoma progression.

Firstly, loss of function study of FAK led to the change of cancer hallmarks which were tumour growth and angiogenesis being evaluated. The authors observed a scientific phenomenon first, then they want to decipher the biological function of FAK contributing to these two cancer hallmarks. Of note, the authors utilized the subcutaneous transgenic mice model Cre-lox recombination to delete FAK labelled as pdgfrβcre+, fakfl/fl mice. Silence of FAK in mice increased tumour volumes and tumour blood vessel density in melanoma and pancreatic insulinoma. Interestingly, knockout of FAK was specific to pericytes other than endothelial cells, mice models demonstrated that loss of FAK from pericytes significantly promoted α-SMA expression (common metastatic biomarker) and NG-2 (typical angiogenesis related biomarker) in three cancer cells model. It suggested that FAK may function as the tumour suppressive gene. However, further validation experiments are needed to draw more precise conclusion.

Secondly, the researchers tend to find the downstream molecular players of FAK for enhancing angiogenesis in cre-lox transgenic mice. Cre-flox mice model eliminated three pro-angiogenic factors such as VEGF, PDGF-B, and PIGF which considered as the general angiogenesis ideology that upregulation of those factors promoted angiogenesis. However, they observed conflicted result which decreased these three common pro-angiogenic factors in response to increased angiogenesis quantified by the upregulation of .α-SMA, the pericytes marker. More questions raised up than the answer at this moment: which factor was required mediating the angiogenesis when deletion of FAK in pericytes *in vivo*? The authors started to suspect Gas6, which is thought to have pro-angiogenic functions. Speaking of Gas6, it is the well-known ligand binding to Axl, inducing proinflammatory cytokine production, enhancing cell proliferation via Ras/MEK-1/ERK signalling, regulating actin reorganization or cell migration through MAPK/P38 pathway and activated PI3K/AKT signalling pathway leading to upregulation of NF-kB, S6K or downregulation of Caspase 3, eventually promoting cells survival [5] etc.

Thirdly, exogenous ligand Gas6 and Axl receptor in pericytes binding increased angiogenesis in FAK null pericytes. It suggested FAK and Axl were two negative correlated molecules and Axl was required for enhanced angiogenesis under the FAK knockout condition. FAK is also known as PTK2 (Protein tyrosine kinase 2), annotated from genecards website (https://www.genecards.org). Protein-protein interaction analysis supported the notion that PTK2 expression was negatively correlated with Axl expression in

411 human samples of bladder urothelial carcinoma and in 375 human samples of stomach adenocarcinoma (Figure 1), data retrieved from ENCORI starbase website [6] (http://starbase.sysu.edu.cn/panGeneCoExp.php).

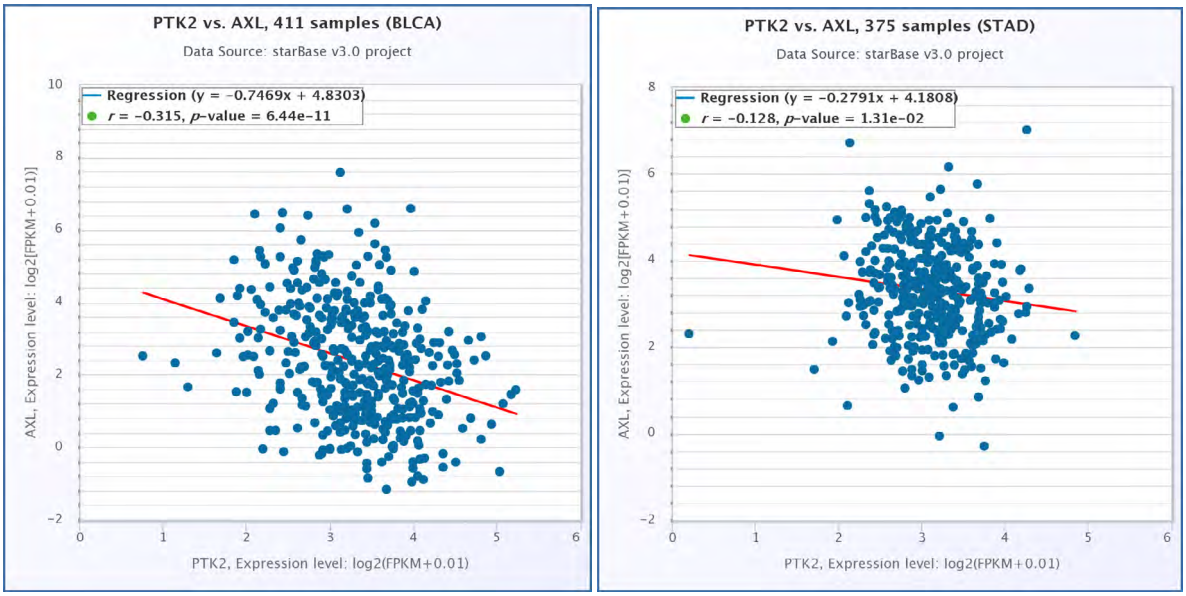

Figure 1: PTK2 expression is negatively correlated to Axl expression in 411 human samples of bladder urothelial carcinoma and in 375 human samples of stomach adenocarcinoma. P value less than 0.05 is considered as significant difference.

Complete knockout of Gas6 by CRISPR-Cas9 [7] system (DNA level, inevitable knockout of certain gene) in melanoma cells rescued tumour growth phenotype in FAK null mice than FAK intact mice. Besides CRISPR knockout technique, we also could use Small Hairpin (shRNA) to stable knockdown the gene of our interest, or Small Interfering (siRNA) to transiently knockdown the gene of our interest. By the same token, double knockout FAK and Axl had the similar result that silence of Axl in FAK^{KO} pericytes reduced the enhanced tumour growth and angiogenesis in mice model. These results further added two pieces of evidence that both Gas6 and Axl were responsible for the enhanced tumour response including tumour growth and angiogenesis when deletion of FAK in mice. To confirm other peers' work, they validated that phosphorylated Pyk2 was elevated under the condition of knockout FAK in pericytes. Suppression of Pyk2 in FAK^{KO} pericytes remarkably diminished Gas6 mRNA expression. It indicated that Pyk2 acted as the linker between FAK and Gas6/Axl signalling pathway.

Fourthly, the authors targeted to understand the effector molecules of Gas6/Axl axis. Exogenous 100nM Gas6 treatment stimulated Cyr61 expression in FAK^{KO} pericytes compared to its counterpart WT pericyte. Within our expectation, deletion of Axl abolished elevated level of Cyr61 caused by Gas6 stimulation, this is the typical rescue experiments. Other publications suggested Cyr61 interacted with integrin on endothelial cells, Axl also can stimulate integrin expression leading to platelet aggregation [4,8]. Endothelial spheroid sprouting assay demonstrated that Cyr61 is pro-angiogenic. Furthermore, complete knockout of Cyr61 in pericytes markedly reduced tumour growth and angiogenesis in FAK null mice. Together, the logic flow of this paper is starting from FAK knockout mice, luckily finding Axl being upregulated as FAK downstream effector, testing the exogenous Gas6/Axl signalling pathway, taking Pyk2 into consideration between FAK and Gas6/Axl, and transitioning to Cyr61, all the factors contributing increased tumour growth and angiogenesis, ending with a graphic abstract: FAK KOà↑Pyk2à↑Gas6/↑Axlà↑Gyr61à ↑tumour growth and ↑angiogenesis.

Last but not the least, to establish the clinical relevance of FAK expression in pericytes and human melanoma. It is worth mentioning that downregulation of FAK positively correlated with the melanoma progression. High numbers of blood vessels especially FAK negative pericytes associated with increased tumour size in human melanoma samples. Therefore, the conclusion deducted from transgenic mice model has better opportunity to transform into clinical setting in the future. Afterall, clinical data are the most persuasive results from first-hand patients' samples. Basic scientific research containing cells culture, genetic manipulation of genes of interest, and various assays to test hallmarks of cancer, along with xenograft mice model served as the combinational methods to have better indicative roles for benefiting the suffering patients in hospital.

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