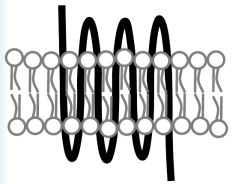
FACULTY OF BIOSCIENCE & BIOINDUSTRY
TOKUSHIMA UNIVERSITY

がん幹細胞の生存戦略に対する持続的制御法の確立

［キーワード：がん幹細胞，成体幹細胞，酸化ストレス］　講師　岸本幸治

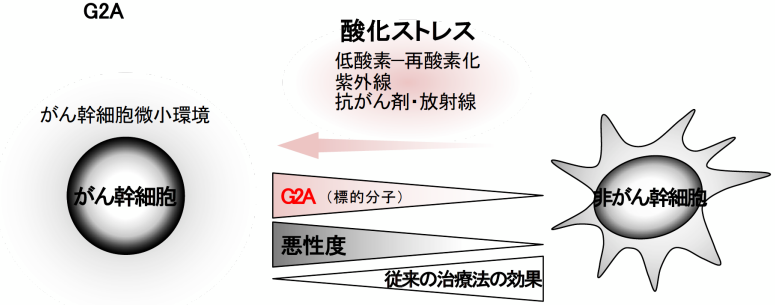
2つの研究を通じて、がん幹細胞の生存戦略を持続的に制御する方法の開発と創薬を目指しています。

新規な抗がん幹細胞治療法および抗がん幹細胞薬の開発

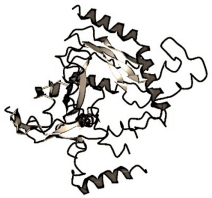


G2A

1. G2A（GPR132)はGタンパク質共役受容体（GPCR）のスーパーファミリーに属する膜受容体です。
2. 酸化脂質やプロトンなどによって活性化されることがわかっています。



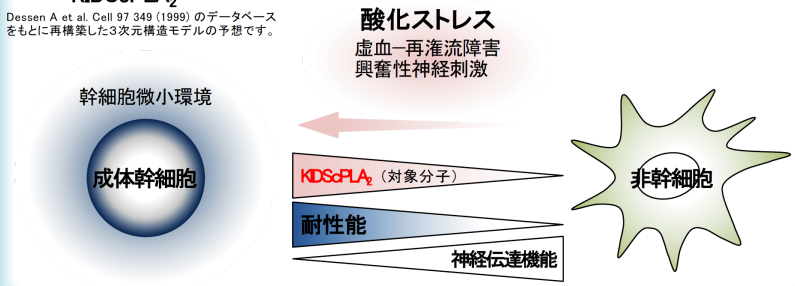
新規神経保護作用薬の開発



KIDScPLA$_2$

Dessen A et al. Cell 97 349 (1999) のデータベースをもとに再構築した3次元構造モデルの予想です。

1. 細胞質型ホスホリパーゼA$_2$α（cPLA$_2$α）の途中から始まるタンパク質構造が興奮性神経伝達刺激によって海馬歯状回に誘導されてくることを見いだしました（KIDScPLA$_2$）。
2. この分子はカルシウム非依存性でPLA$_2$活性を消失していますが成体幹細胞が存在する多くの特異的組織領域に、酸化ストレスによって誘導され、細胞保護することがわかりました。



内容：

iPS細胞など未分化細胞の分化誘導の際に起こってしまうがん化は再生医療の安全性をおびやかしています。19世紀、「がんは、何らかの刺激により組織が損傷され、その局所炎症から生じる。」とウィルヒョウが唱えたように、正常幹細胞や非がん細胞は慢性炎症などに起因する酸化ストレスによってがん幹細胞化(幹細胞性の誘導)し、悪性化、生存維持することも示されています。加えて、多くのがんの発生・再発・転移がこのがん幹細胞を原因としておこっていることからがん治療では注目すべき標的細胞なのですが、生体中の正常幹細胞とも局在や性質において類似点が多く、このことも、がん幹細胞に対する標的治療法開発を困難にしています。これらの背景から、がん幹細胞がどのような機序で誕生し、長期に生存維持できるのかについて明らかにすることは喫緊の課題です。私たちは細胞の分化・脱分化の過程で起こる細胞のがん化や悪性化の仕組みを明らかすること、がん幹細胞に特異的な機能分子を見いだし、難治性がんに対する治療法を開発することを目的として研究を進めています。酸化ストレスによって誘導・活性化される特定の膜受容体と脂質代謝酵素に由来する新規タンパク質を見いだし、過剰なストレスにさらされた際にがん幹細胞や成体幹細胞の発生・生存維持をこれらの分子が制御している可能性を見いだしました。これらの機序解明によってがんの発生・再発・転移を低減させる持続的治療法の開発と創薬を目指し、再生医療の安全性向上に寄与します。

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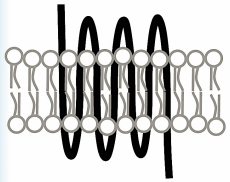
Establishment of Sustainable Control of Cancer Stem Cells

Associate professor Koji Kishimoto

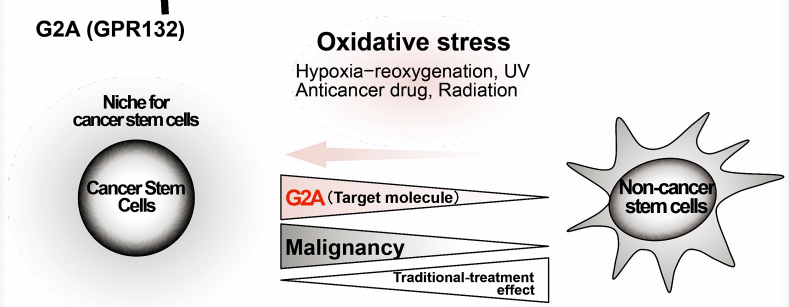
We are dedicated to the following studies, which contribute to the low risk and peace of mind associated with regenerative medicine.

Development of Novel Effective Treatments Toward Cancer Stem Cells

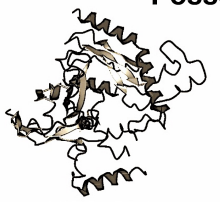


G2A (GPR132)

1. G2A (GPR132) is a membrane receptor belonging to G-protein coupled receptor (GPCR) superfamily.
2. G2A is activated with oxidized fatty acids and proton.



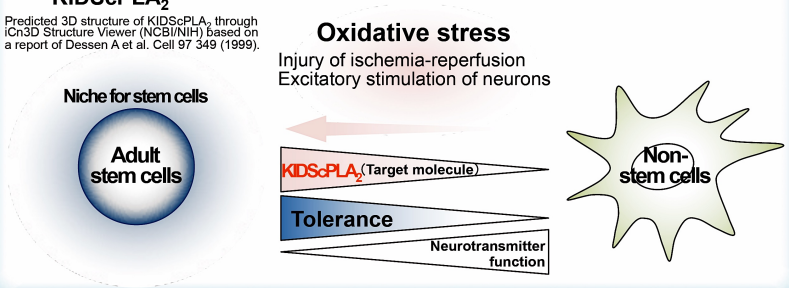
Development of Novel Drugs Possessing Neuroprotective Action



$KIDScPLA_2$

Predicted 3D structure of $KIDScPLA_2$ through iCn3D Structure Viewer (NCBI/NIH) based on a report of Dessen A et al. Cell 97 349 (1999).

1. Neuronal excitation induced a truncated mRNA covering from the 10th exon to the final exon on cytosolic phospholipase $A_2\alpha$ ($cPLA_2\alpha$) ($KIDScPLA_2$) in the dentate gyrus dramatically.
2. $KIDScPLA_2$ protein hardly showed PLA_2 activity and was induced in specific tissue regions, where were potential ones in which adult stem cells were found.



Introduction:

Regenerative medicine presents many promising opportunities, but is not without potential risks. The purposeful manipulation of unspecialized cells, such as induced pluripotent stem cells, has contributed greatly to the development of regenerative medicine. However, these manipulations may also facilitate unintended consequences, such as the accumulation of unrepaired malignant alterations. Many questions concerning both malignant alteration of unspecialized cells and malignant dedifferentiation of cells remain unanswered despite substantial research efforts. Additionally, parallels between normal stem cells and cancer stem cells further complicate the development of new medical treatments targeting cancer stem cells. Therefore, we hope to elucidate the molecular mechanisms underlying stem cell malignant transformation, with the ultimate aim of developing effective treatments and novel drugs targeted towards cancer stem cells. We also believe that our study will help develop a mechanism whereby reoccurrence and metastasis can be halted following treatment, enhancing the potential for these treatments to be successful. The 19th century German pathologist R. L. Virchow highlighted the importance of inflammatory stimulation in cancer with his chronic irritation theory: cancer is caused by severe irritation in the tissues and arises from the activation of dormant cells. We propose that this theory can be applied to better understand the pathogenesis of cancer stem cells.

With this understanding, we have identified a cell membrane receptor and a protein derived from a lipid-metabolizing enzyme that are both activated by oxidative stress to regulate the initiation and maintenance of cancer stem cells. We are now investigating the utility of this system for efforts to bring the tumorigenic capacity of cancer stem cells under control. We are also further refining our understanding of the mechanisms involved. We believe that this work will aid the development of novel treatments and drugs that will mitigate the risks of malignant alteration of unspecialized cells during reprogramming and malignant dedifferentiation of cancer cells.

Lipid metabolism in stem cells is emerging as an important mechanism of control for stem cells and the stem cell niche. Given the close associations between oxidation and lipid metabolism, we are enthusiastic about the prospects of this work to yield an innovative breakthrough in the control of cancer stem cells.

Keywords : <cancer stem cells, oxidative stress>

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