La voie de l'EGF dans la polypose adénomateuse familiale : intérêt du modèle d'organoïdes coliques humains

N Laborde, A Barusseaud, M Quaranta, D Bonnet, S Kirzin, L Alric, K Barange, JP Duffas, A Breton, N Vergnolle, A Ferrand, C Racaud-Sultan, E Mas

CHU Toulouse - Institut de Recherche en Santé Digestive

Hôpital des Enfants

Hôpitaux de Toulouse

UNIVERSITÉ TOULOUSE III PAUL SABATIER

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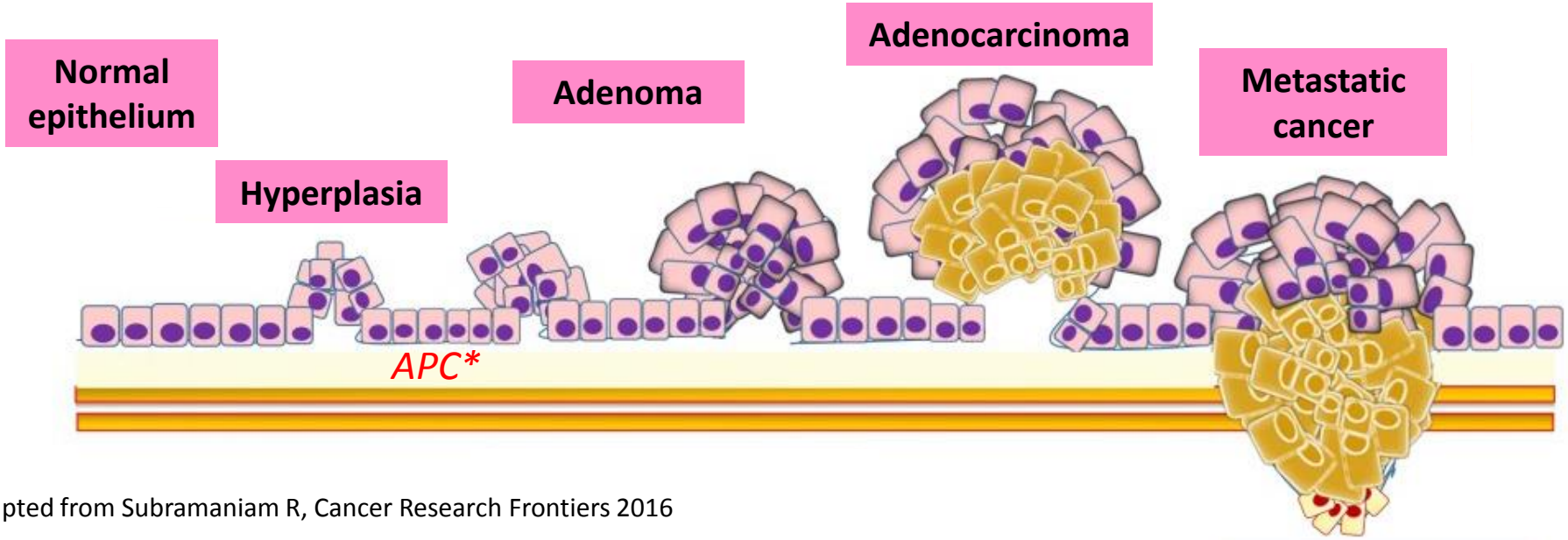
CONTEXTE

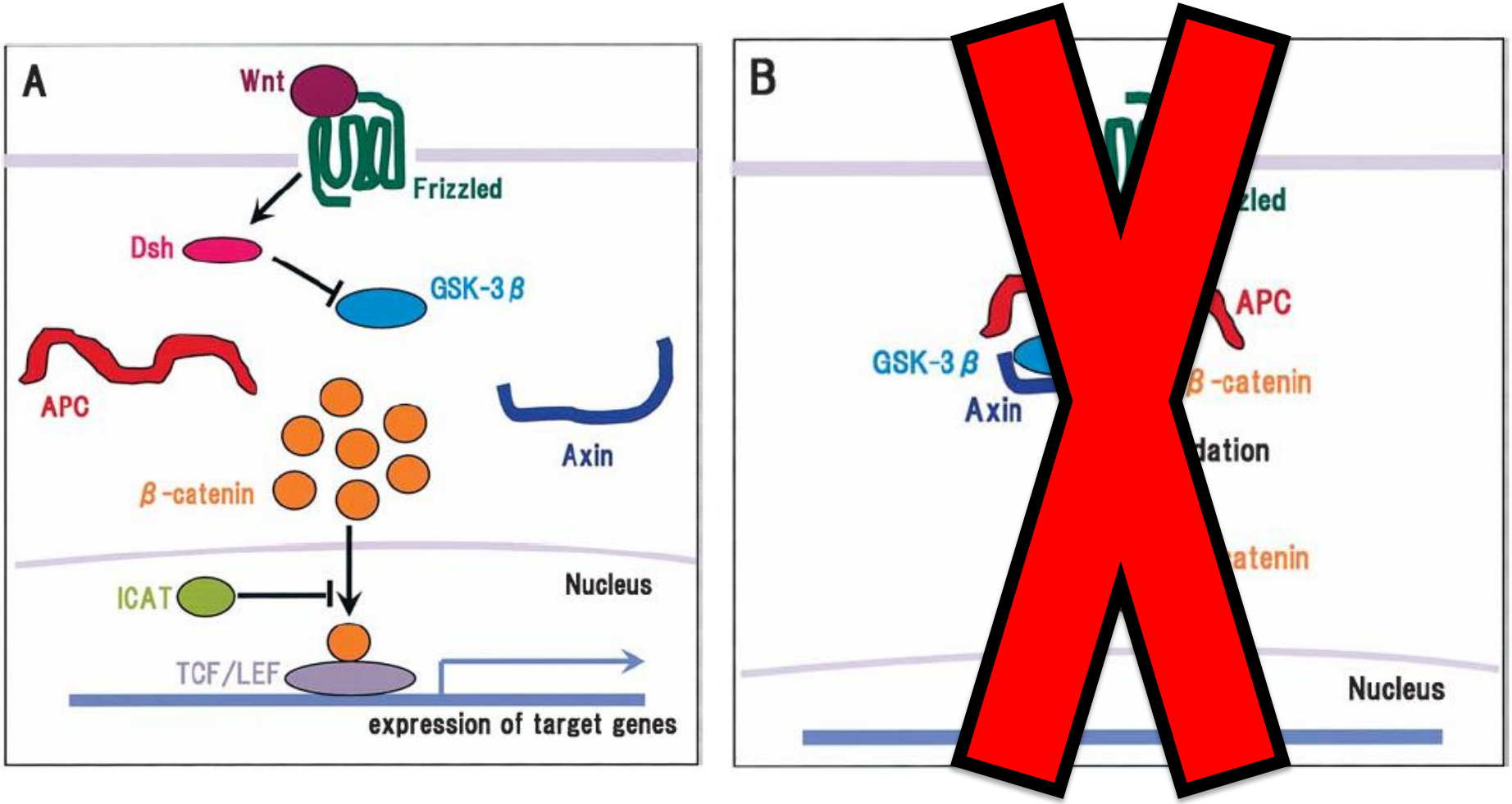
- **Polypose adénomateuse familiale (PAF):**
  - mutations du gène *APC* (gène suppresseur de tumeur)
  - Prévalence = 1/10 000
  - Responsable de 1% de cancers colorectaux

- Polypes adénomateux ➔ **Cancer colorectal +++**



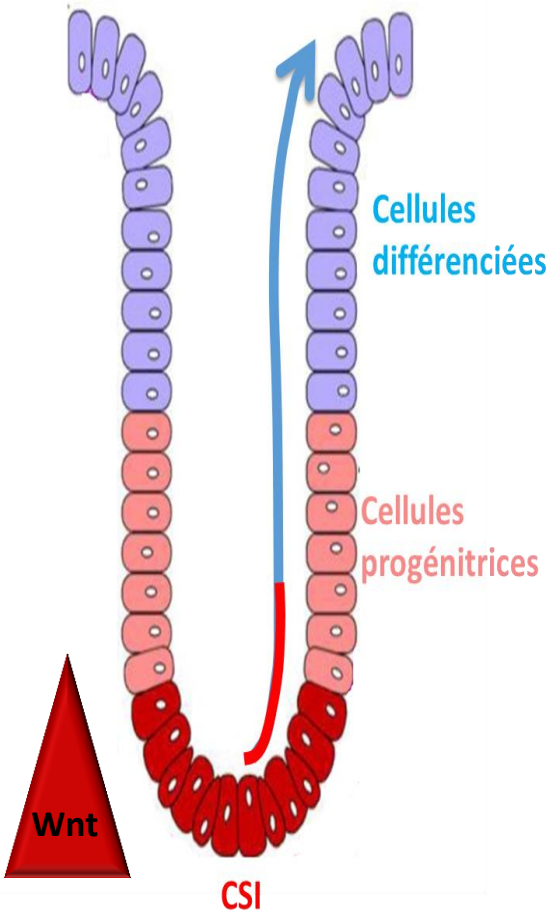
Adapted from Subramaniam R, Cancer Research Frontiers 2016

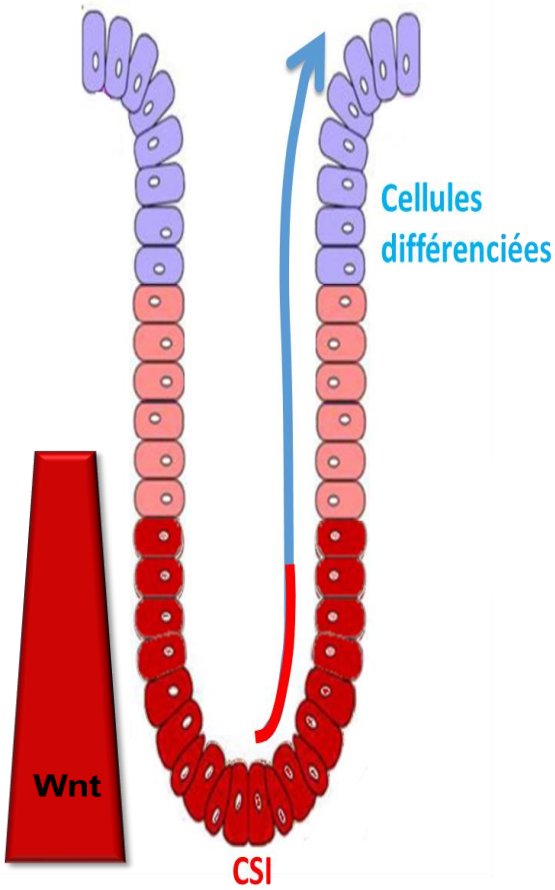
Voie Wnt/APC/β-caténine

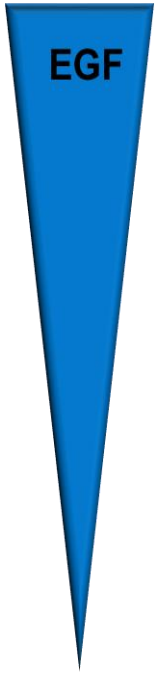


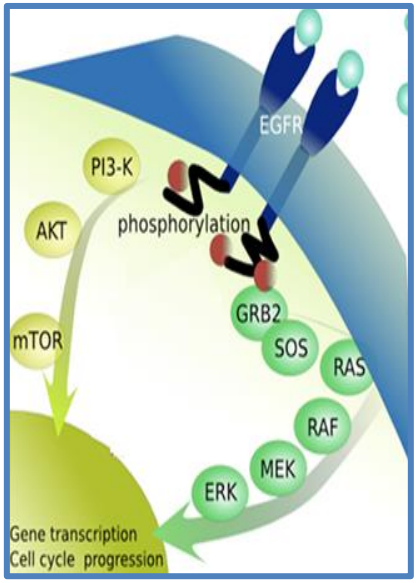
PAF = activation des cellules souches intestinales (CSI)

PAF = atteinte cellules souches intestinales







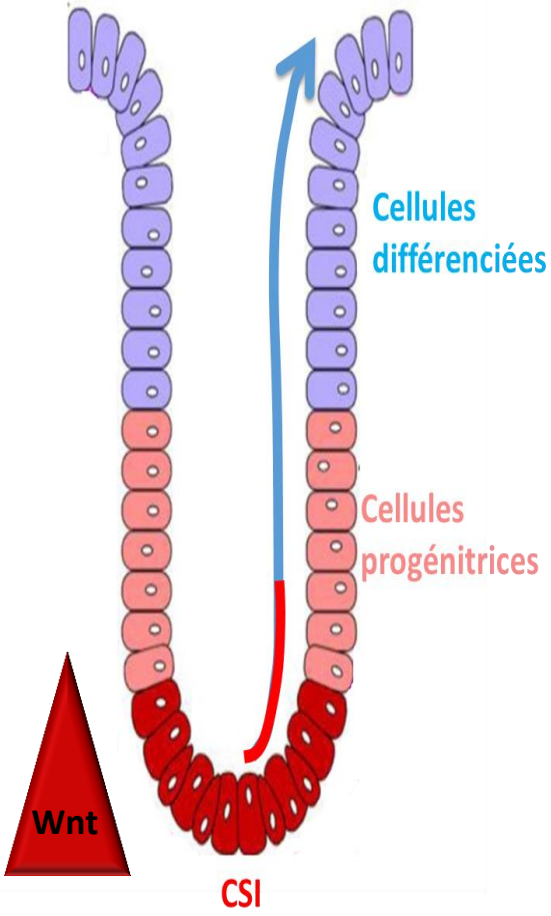


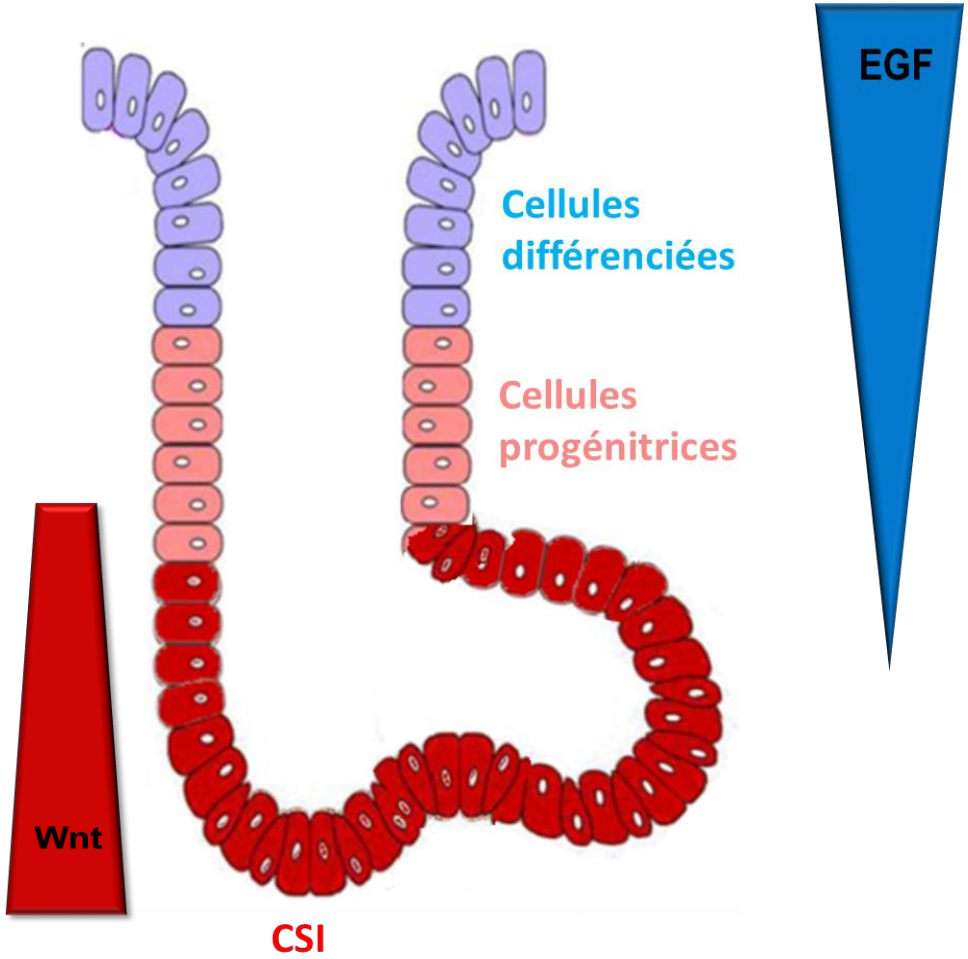
Prolifération
Migration
Différentiation

Contrôles sains

Patients PAF

PAF = rôle de l'EGF ?





Contrôles sains

Patients PAF

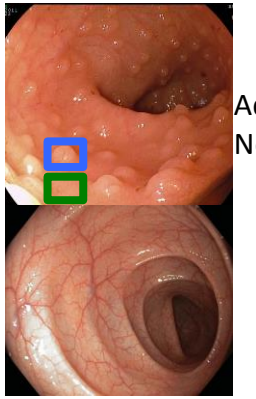
PATIENTS ET METHODES

- **Organoïdes coliques humains :**
  - Modèles animaux (dont murins) non relevants
  - Modèle idéal pour étudier les propriétés des CSI

- **Etude :**

Patients PAF (n=18)

Témoins sains (T, n=11)

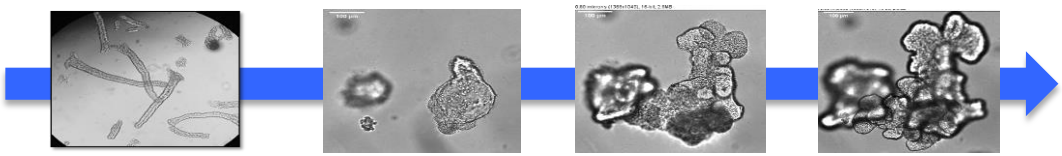


Adénomateux (A)
Non adénomateux (NA)

Isolement des cryptes

Culture d'organoïdes 3D dans matrigel

Milieu de culture
ADF, Glutamax, Hepes, N2, B27, **EGF**, Noggin, ± **Wnt3a**, R-spondin, NAC, Nicotinamide, Gastrine, SB202190, PGE2, LY2157299



J0 **J2** **J5** **J7**

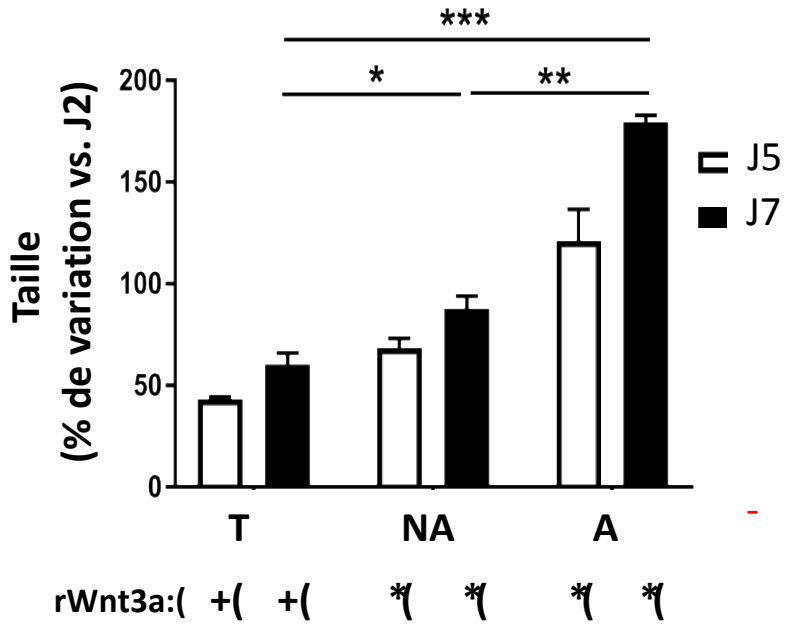
Retrait Wnt3a (PAF)

Retrait EGF

Ethic committee approval (BIODIGE, 2016-A00016-45)

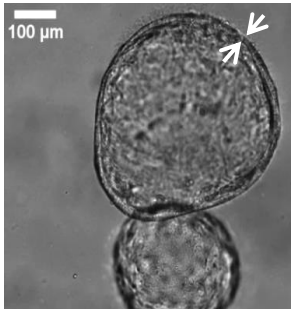
Adapted from Jung et al. Nature Medicine 2011

RESULTATS: morphologie et croissance

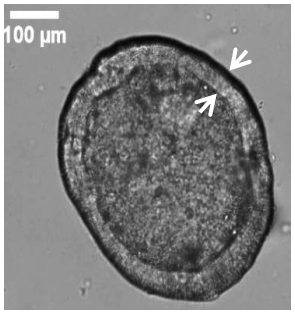


Organoïdes précédemment décrits :

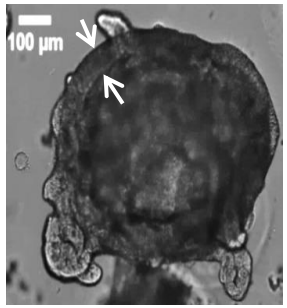
Cyste



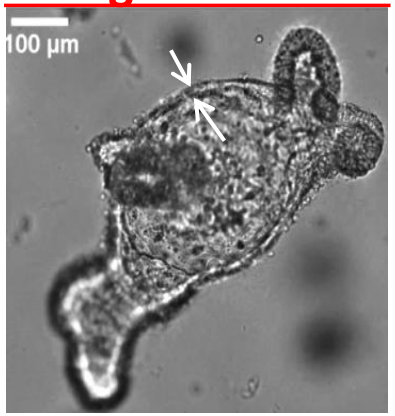
Colonosphère



Colonoide



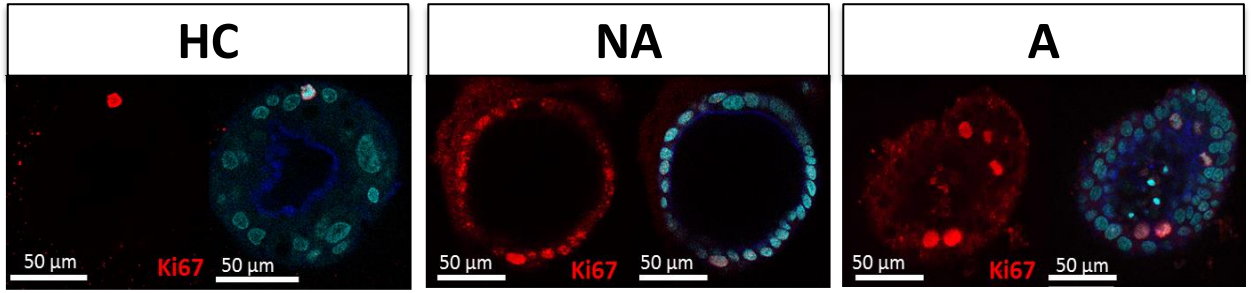
Cyste avec bourgeonnement

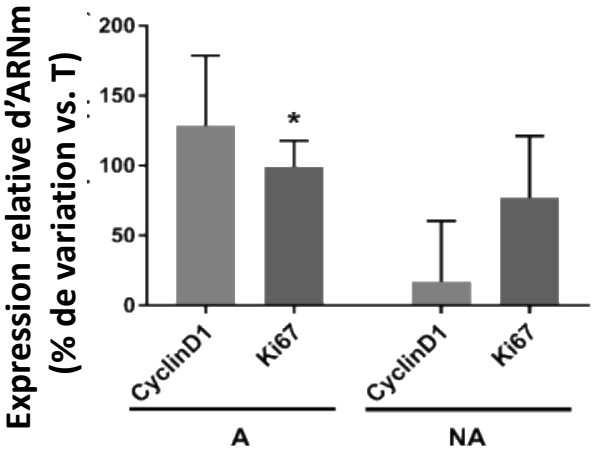


➔ **Caractérisation d'un nouveau type d'organoïde mimant l'adénome reproduit en 3D**

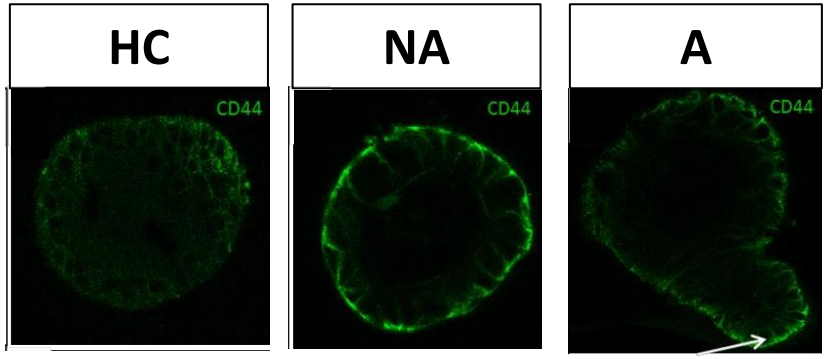
RESULTATS : prolifération et immaturité

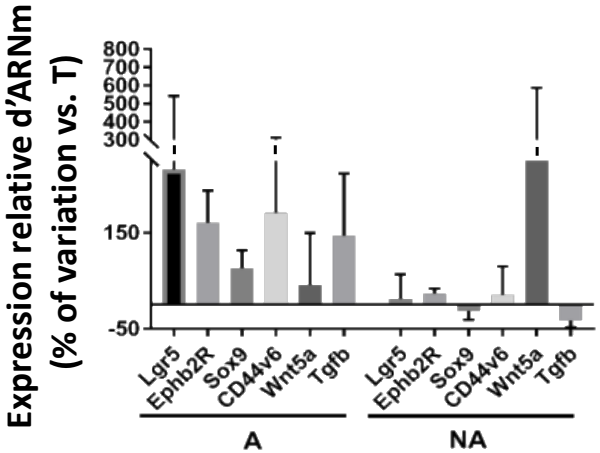
Prolifération (Ki67)



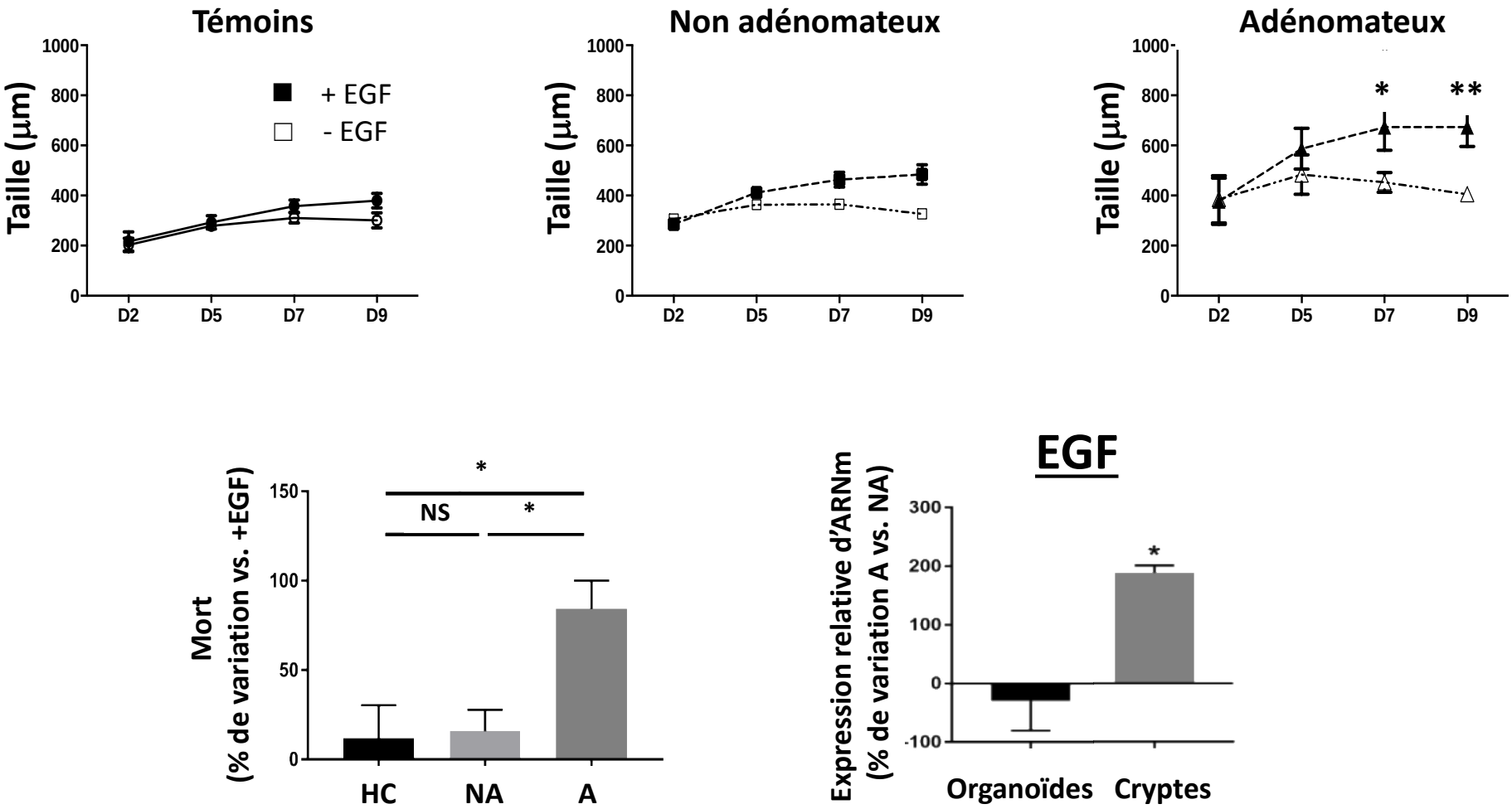


Immaturité (CD44)



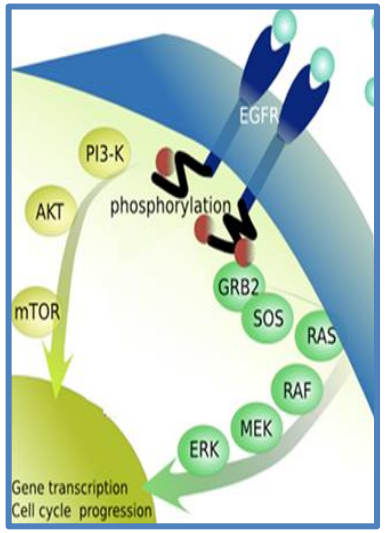


RESULTATS : voie de l'EGF

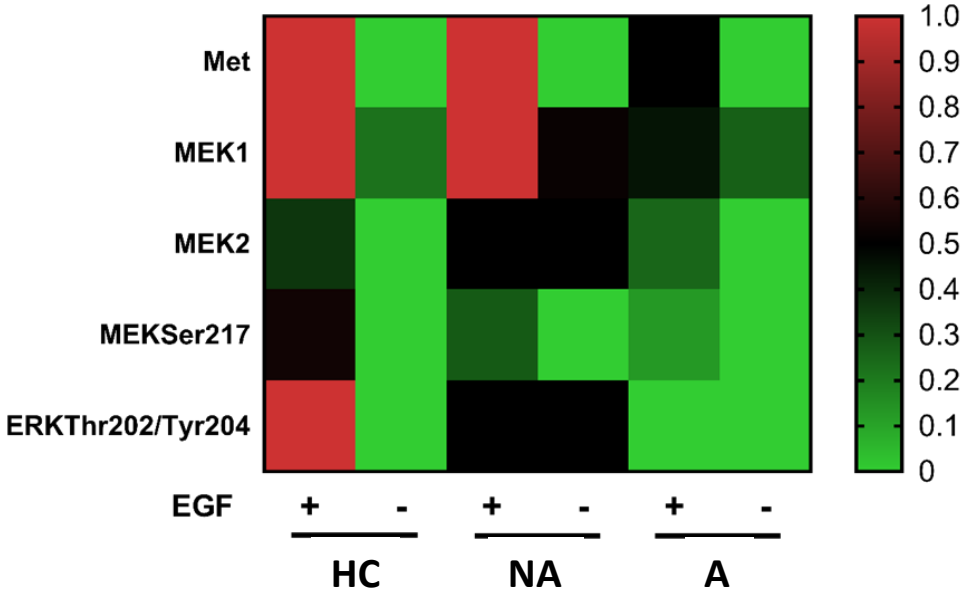


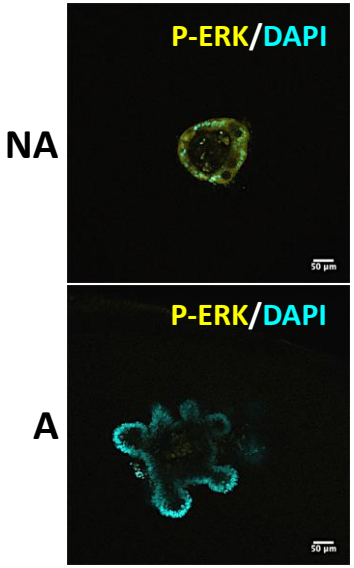
➔ **Importance de l'EGF, facteur clé dans les tissus adénomateux**

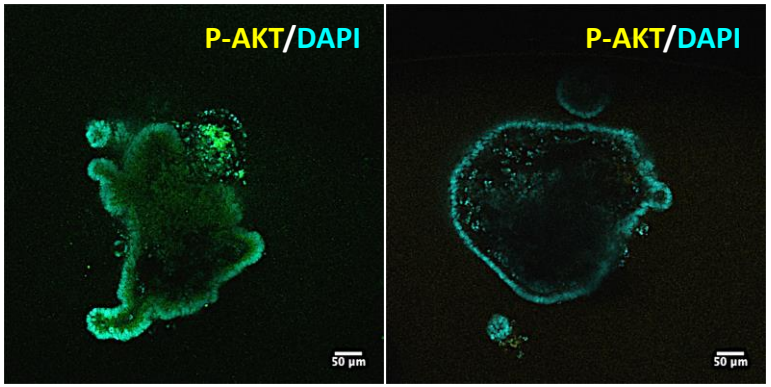
RESULTATS : voie de l' EGF (2)

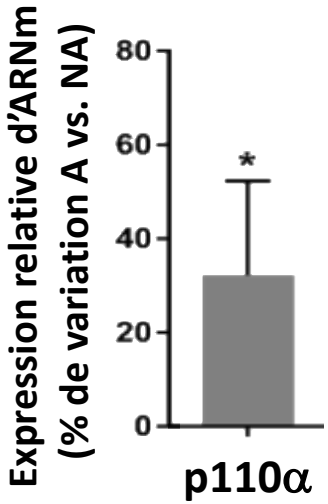


Expression des protéines de la voie de l'EGF (J7)



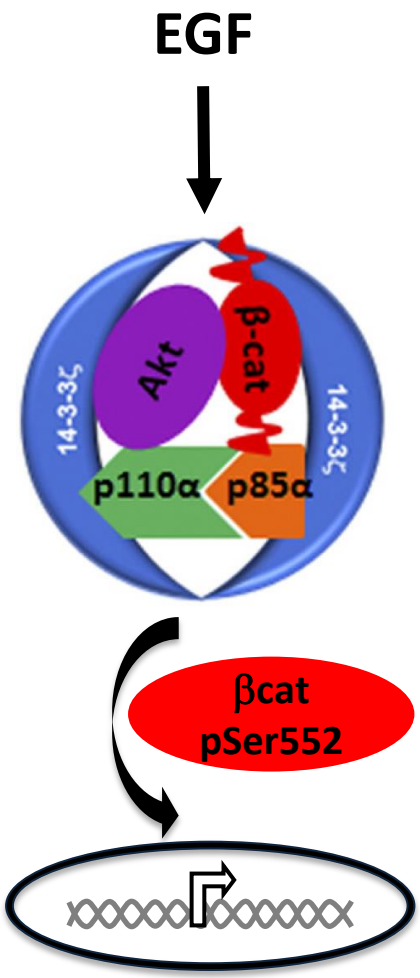




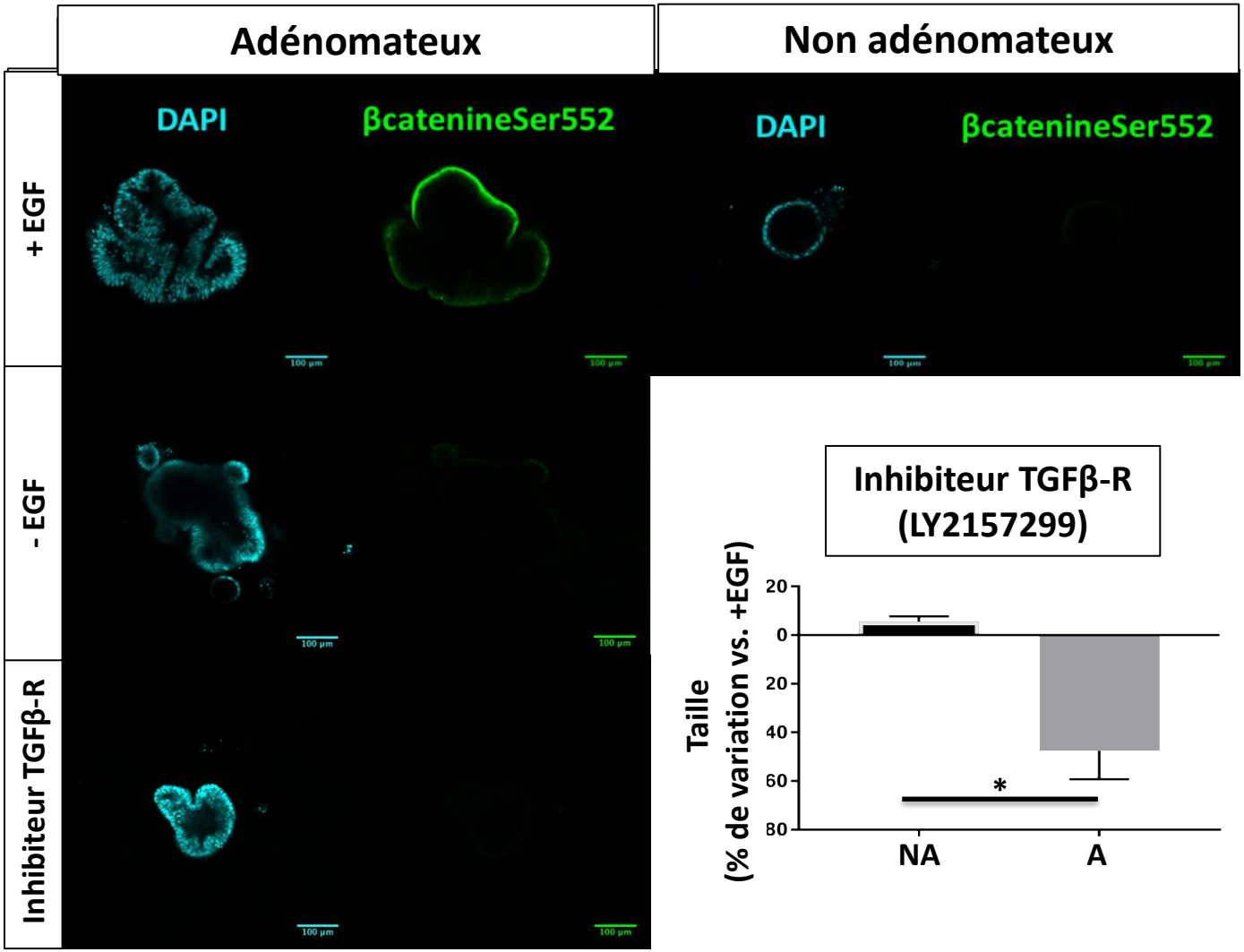


➔ **Dans les adénomes, la régulation via EGF se fait spécifiquement par la voie PI3-K/Akt**

RESULTATS : implication de PI3K / Akt

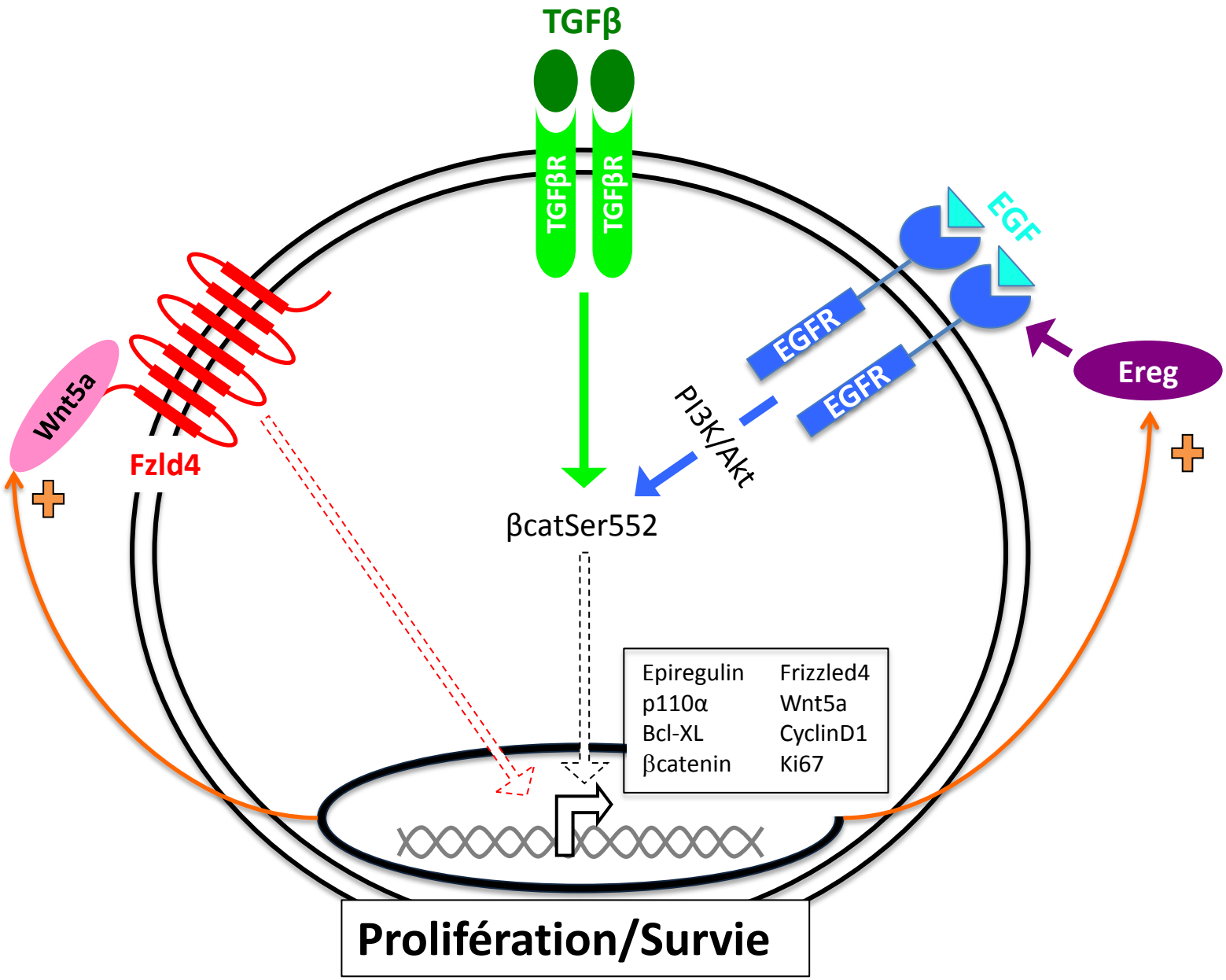


Adapted from Goretsky T, J Biol Chem 2016



➔ La phosphorylation de β-catenin Ser552 est contrôlée par EGF and TGFβ

Résumé : CSI adénomateuses



Conclusion

- **Caractérisation d'une forme d'organoïdes spécifiques dans la PAF : cyste avec bourgeonnement ≈ adénome**

- **Différences entre A and NA:**
  - Adénomateux = EGF (PI3K/Akt) et TGFβ
  - Non adénomateux = EGF (MAPK)