

Literature Report

Reporter: Bao Fang

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Highly efficient intercellular spreading of protein misfolding mediated by viral ligand-receptor interactions

Shu Liu,^{1,10} André Hossinger,¹ Stefanie-Elisabeth Heumüller,¹ Annika Hornberger,¹ Oleksandra Buravlova,¹ Katerina Konstantoulea,^{2,3} Stephan A. Müller,^{4,5} Lydia Paulsen,¹ Frederic Rousseau,^{2,3} Joost Schymkowitz,^{2,3} Stefan F. Lichtenthaler,^{4,5,6} Manuela Neumann,^{7,8} Philip Denner,¹ and Ina M. Vorberg^{✉1,9}



Introduction



1989-1995 Microbiology
Eberhard-Karls-University, Tübingen

1996-1996 Dr. rer. nat.
Eberhard-Karls-University, Tübingen

1996-1999 Graduate Student
Tübingen, The Federal Research Centre for Virus Disease of Animals

1999-2003 Postdoctoral
The Laboratory of Persistent Viral Diseases at the National Institutes of Health
National Institute of Allergy and Infectious Diseases
Rocky Mountain Laboratories, USA

2004-2006 Junior research group leader
The Institute of Virology, TU Munich

2006-2010 Independent research group leader
The Institute of Virology, TU Munich

2010- Research group leader
DZNE Bonn

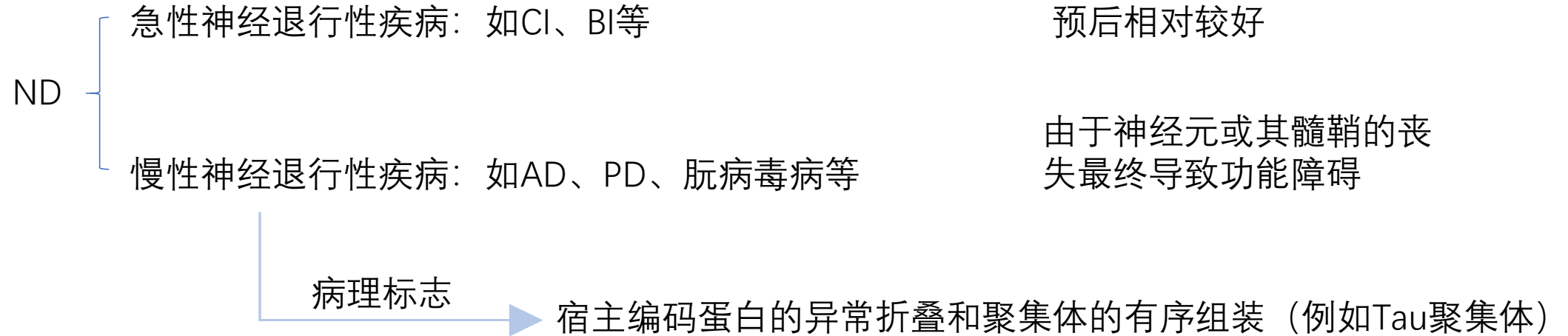
研究方向:

1. The molecular and cellular mechanisms involved in prion formation.
2. cellular pathways involved in intercellular aggregate dissemination.

Dr. Philip Denner

1. Bayer: early drug discovery
2. Laboratory Automation Technologies (LAT) of DZNE service:
 1. Laboratory Automation
 2. Image Analysis
 3. High-Content Screening
 4. Protein Aggregation

Introduction

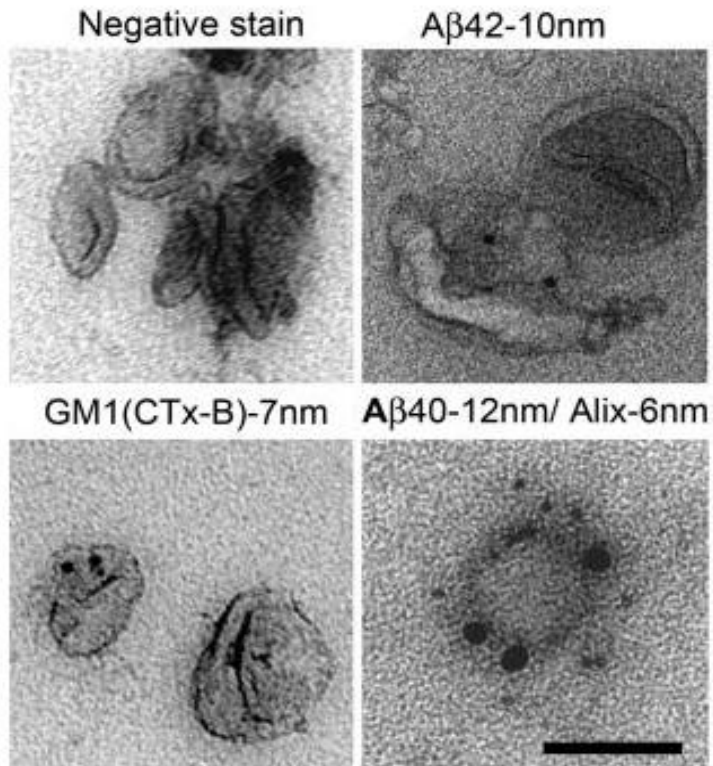


疾病相关的蛋白质聚集体通过某些途径在细胞间传递，从而将自身异常构象模板到可溶性同型蛋白中，扩大病变范围[1]。

目前主要认为有三种途径：

- 1.游离的蛋白质病性聚集体种子释放到细胞外；
- 2.EV转运活性蛋白质病性聚集体种子；
- 3.借助细胞膜的结合和融合直接传递蛋白质病性聚集体种子。

Introduction



β 淀粉样肽 (A β) 是AD进展中的一种蛋白质病性聚集体，可以同EV同时向细胞外释放，从而感染周围细胞[2]。

Introduction



病毒糖蛋白是否可以通过EV途径等受-配体作用模式将蛋白质病性种子传递到细胞外，从而实现种子的胞间传递？



1.Expression of viral glycoprotein VSV-G drastically increases cell-to-cell spreading of cytosolic prions.

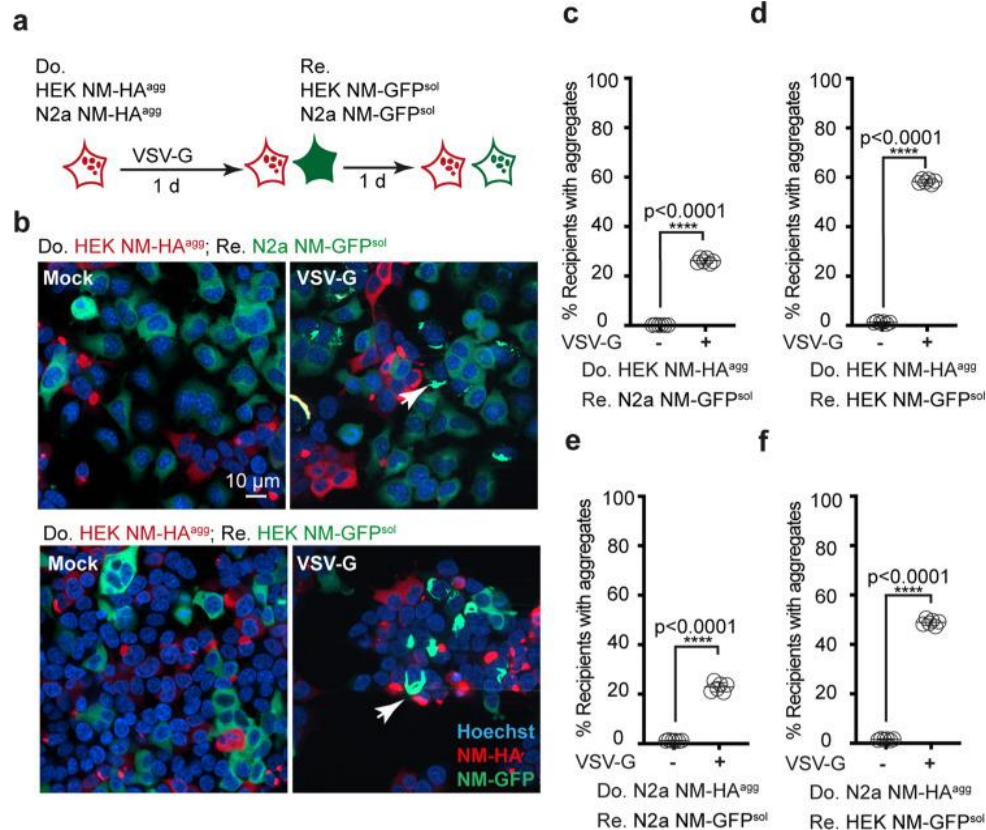


酿酒酵母Sup35翻译终止因子中朊病毒蛋白质性质:

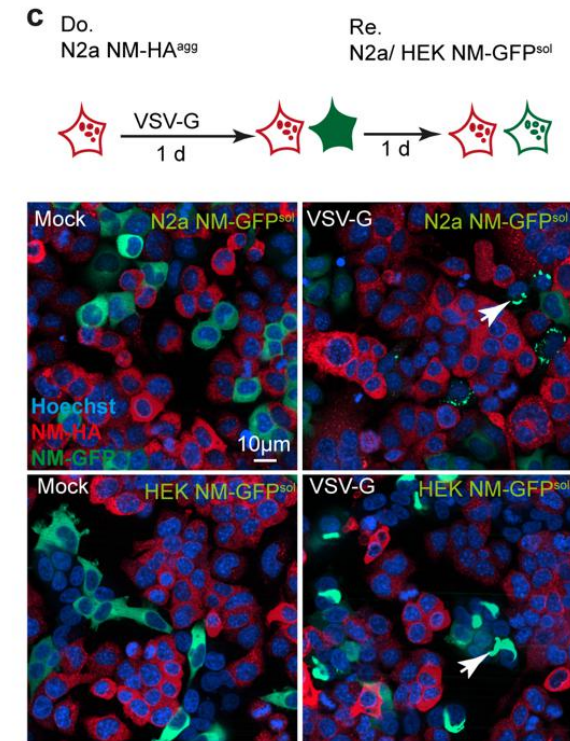
- 1.存在功能可溶性亚型;
- 2.可以将其蛋白质构象印记到同型可溶性蛋白中进行自我复制;
- 3.朊病毒结构域NM具有蛋白质聚集能力。

VSV-G是水疱性口炎病毒的糖蛋白，由于其糖蛋白为表面蛋白，常用作慢病毒载体。受体为LDL。

Fig1



Suppl. figure 2





1.Expression of viral glycoprotein VSV-G drastically increases cell-to-cell spreading of cytosolic prions.



Suppl. figure 2

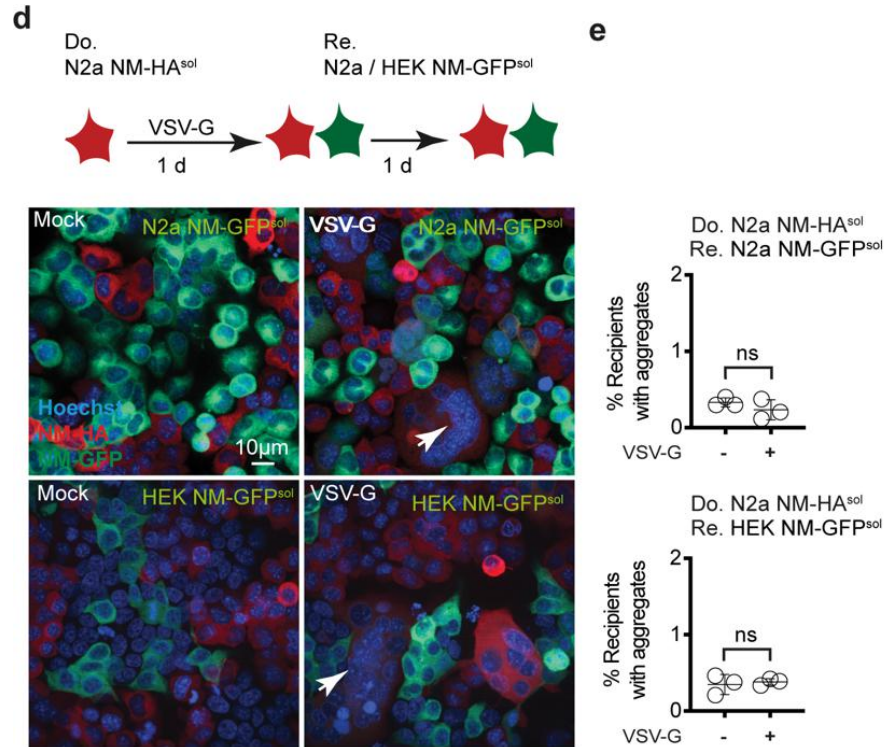
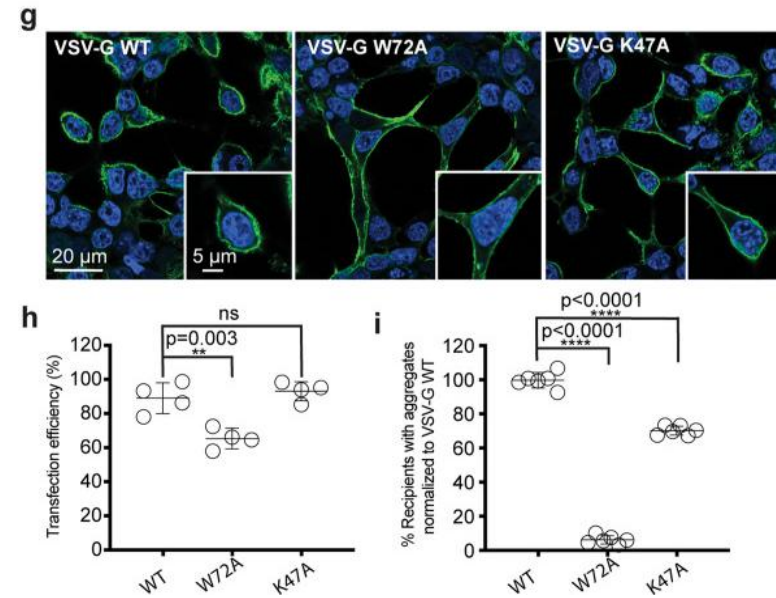


Fig1



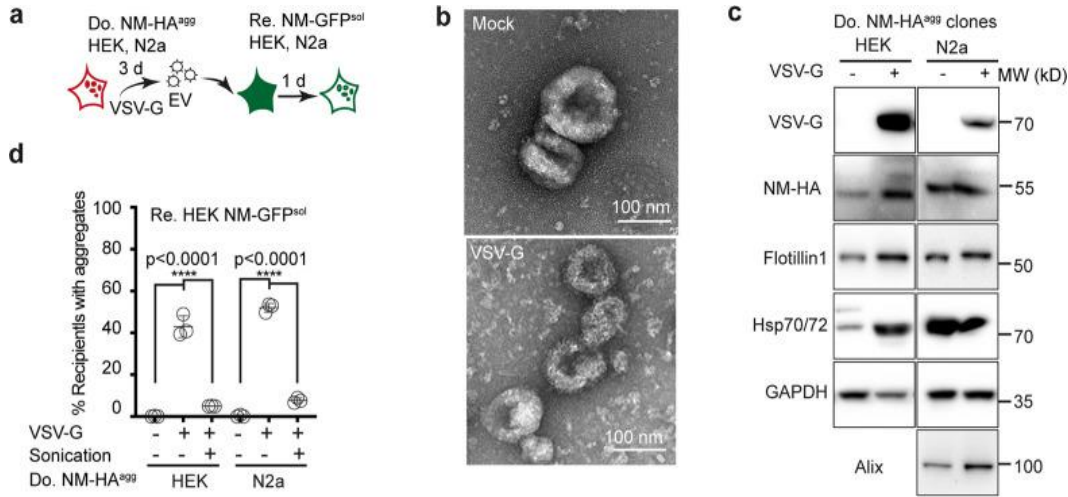
有一部分膜融合传播途径独立于 LDL 同 VSV-G 的配受体结合



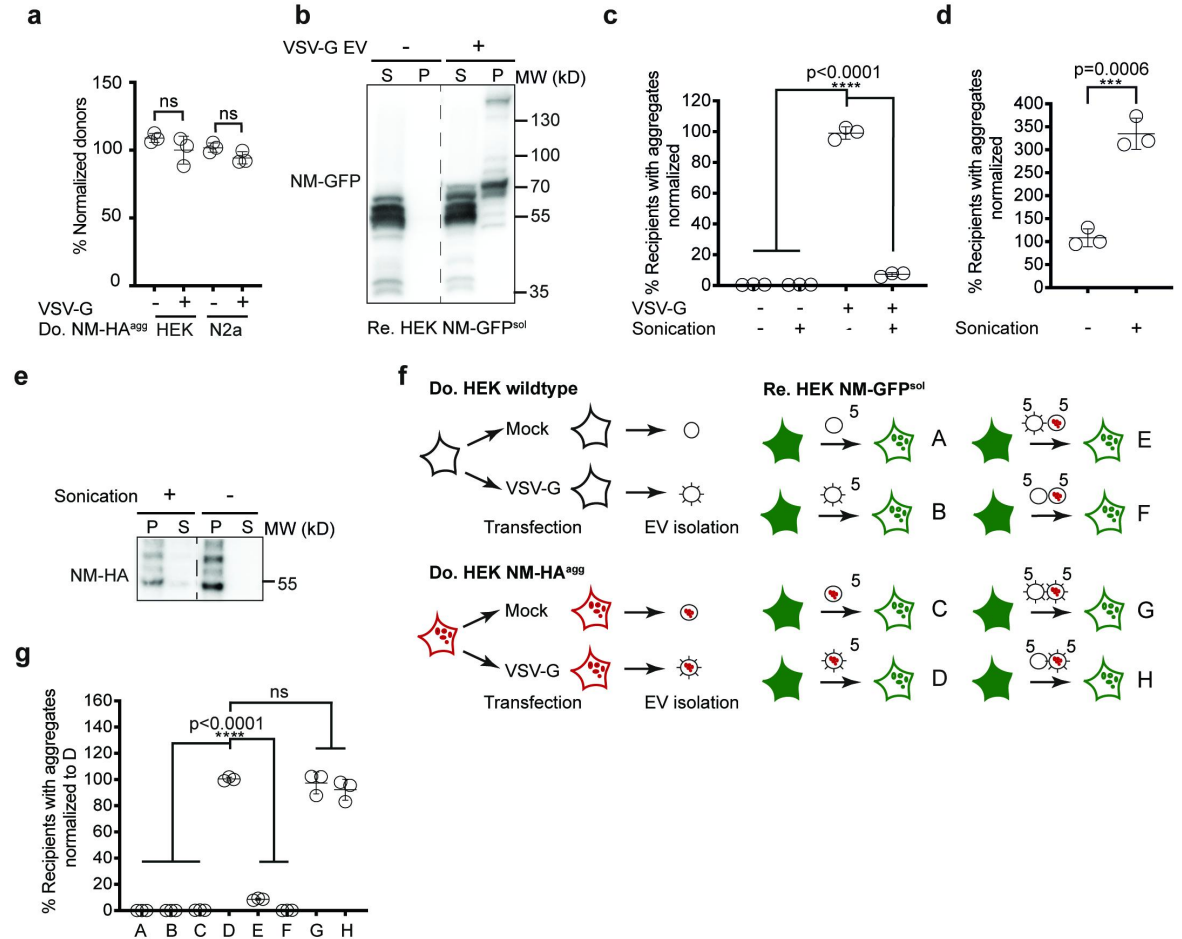
2.VSV-G mediates efficient vesicular dissemination of cytosolic NM prions



Fig 2



Suppl. figure 3



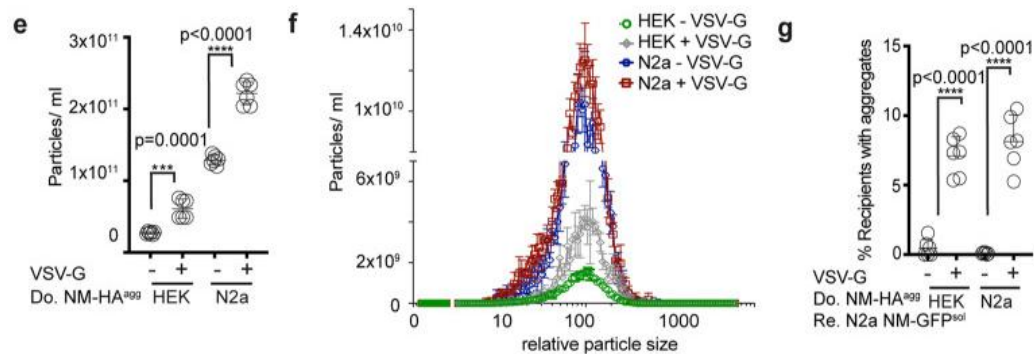
VSV-G修饰的完整EV是朊病毒蛋白质病性聚集体种子传播所必需的。



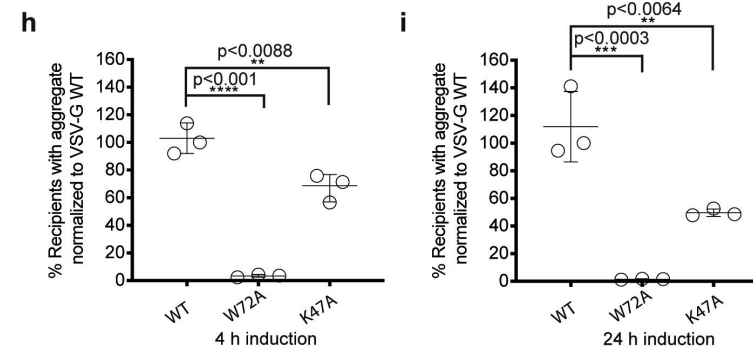
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Fig 2



Suppl. figure 3



VSV-G诱导聚集体的能力可能与提高产生EV的能力有关

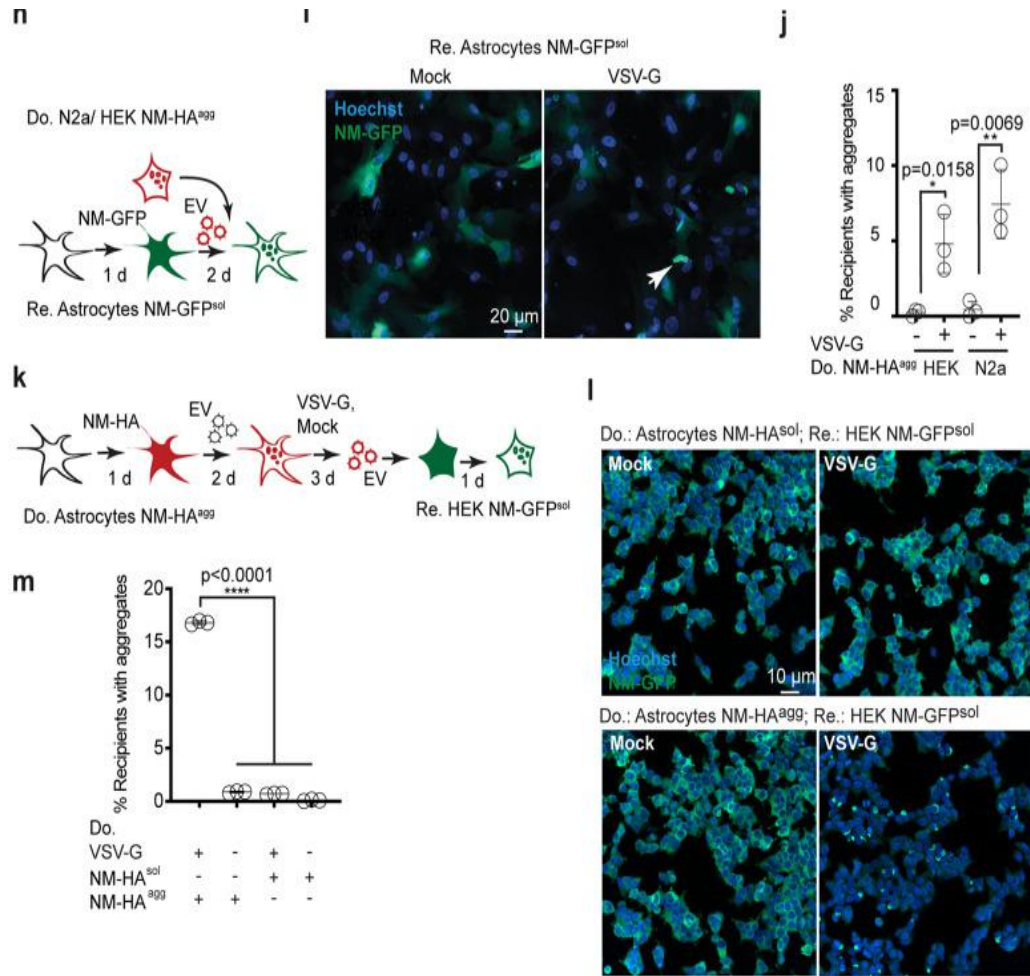
VSV-G修饰的完整EV有其他的受体和摄取途径



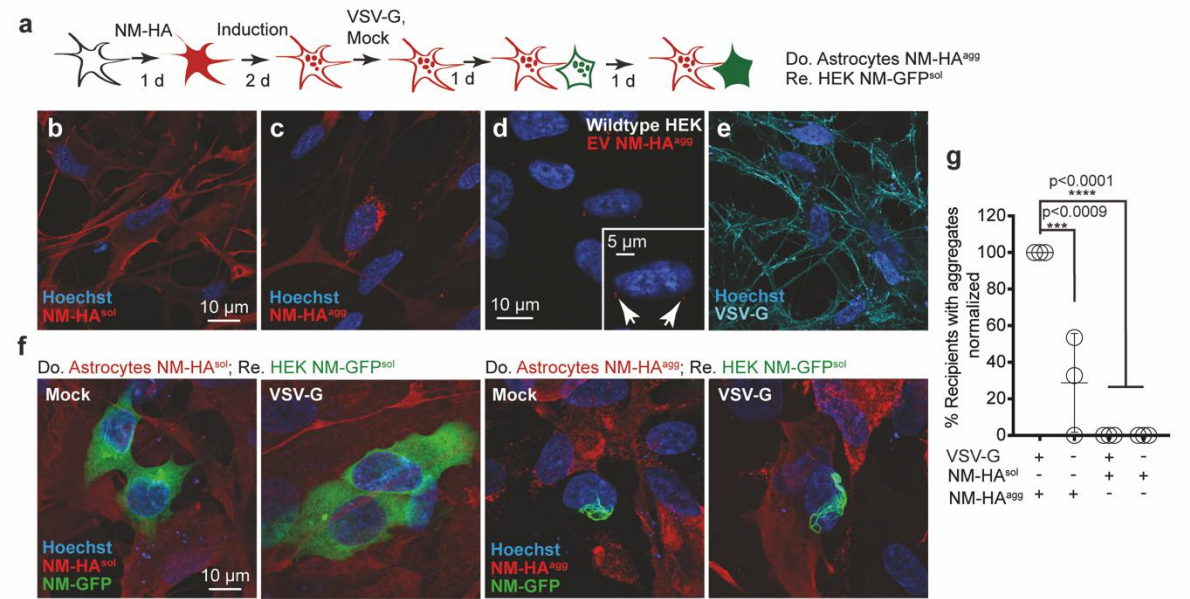
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Fig 2



Suppl. figure 4



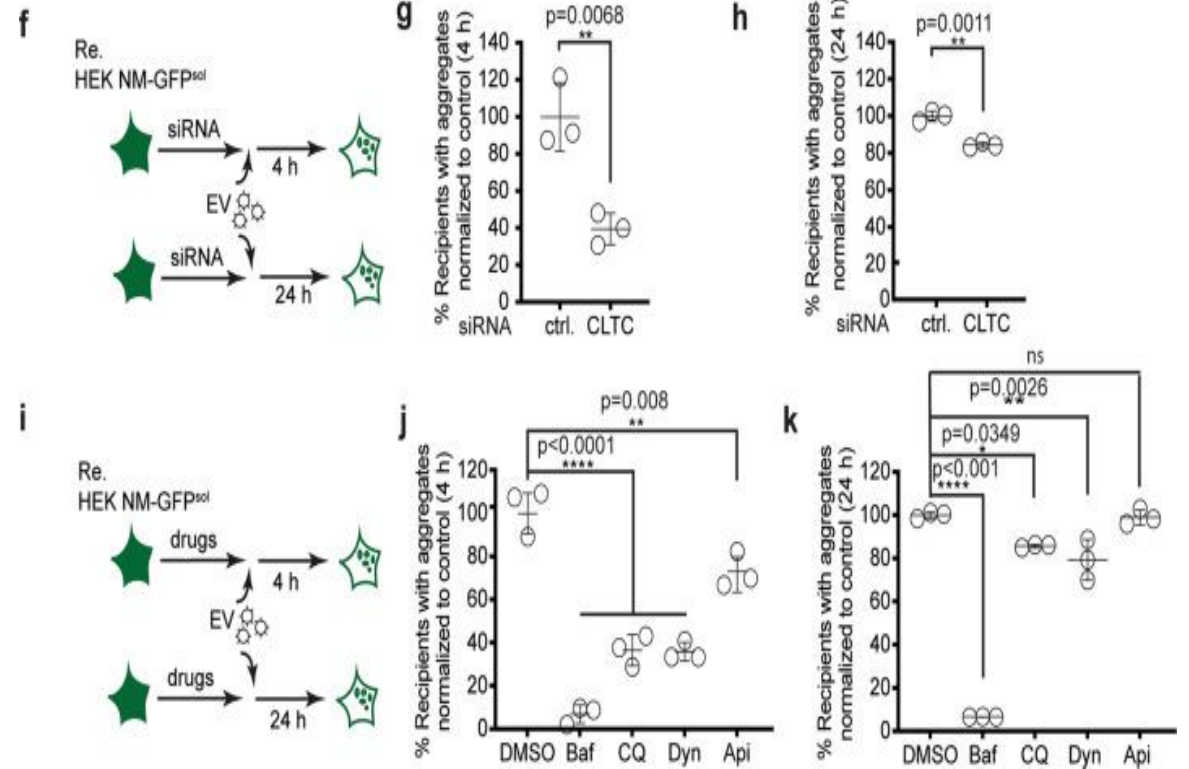
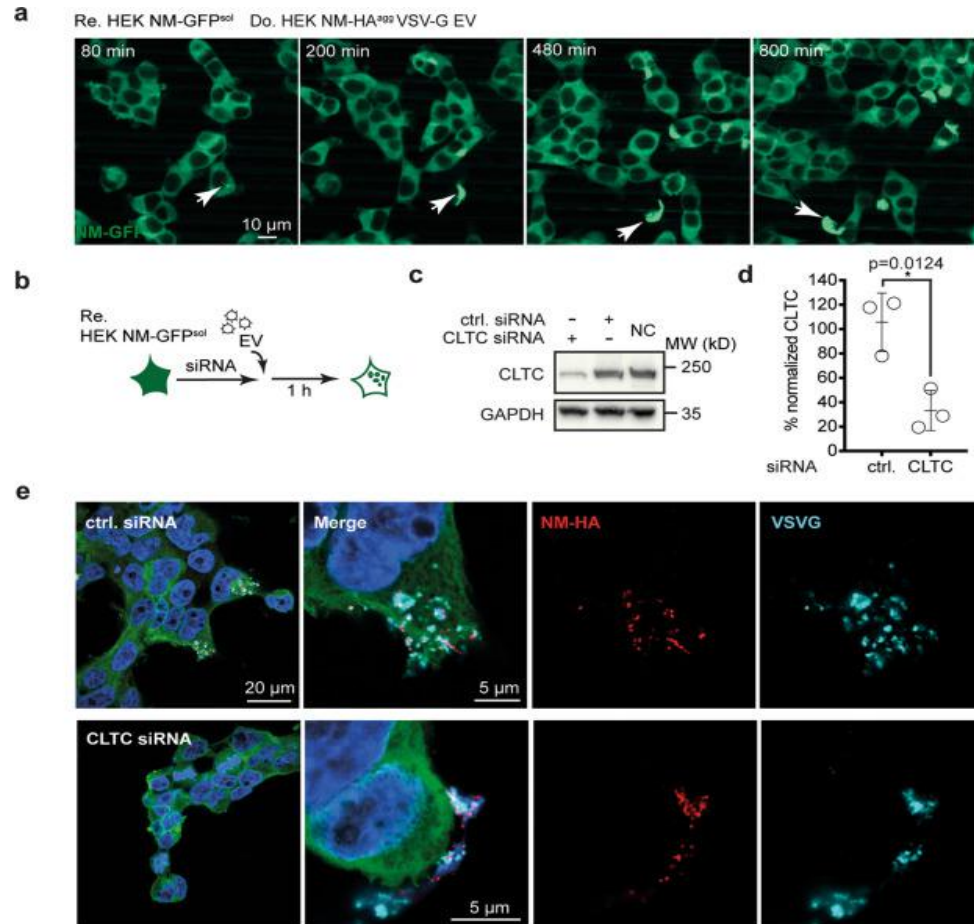
VSV-G也可增强原代细胞中细胞间的聚集诱导



3. VSV-G-pseudotyped EV preferably enter cells by clathrin-mediated endocytosis and fuse at low pH for endosomal escape.



Fig 3



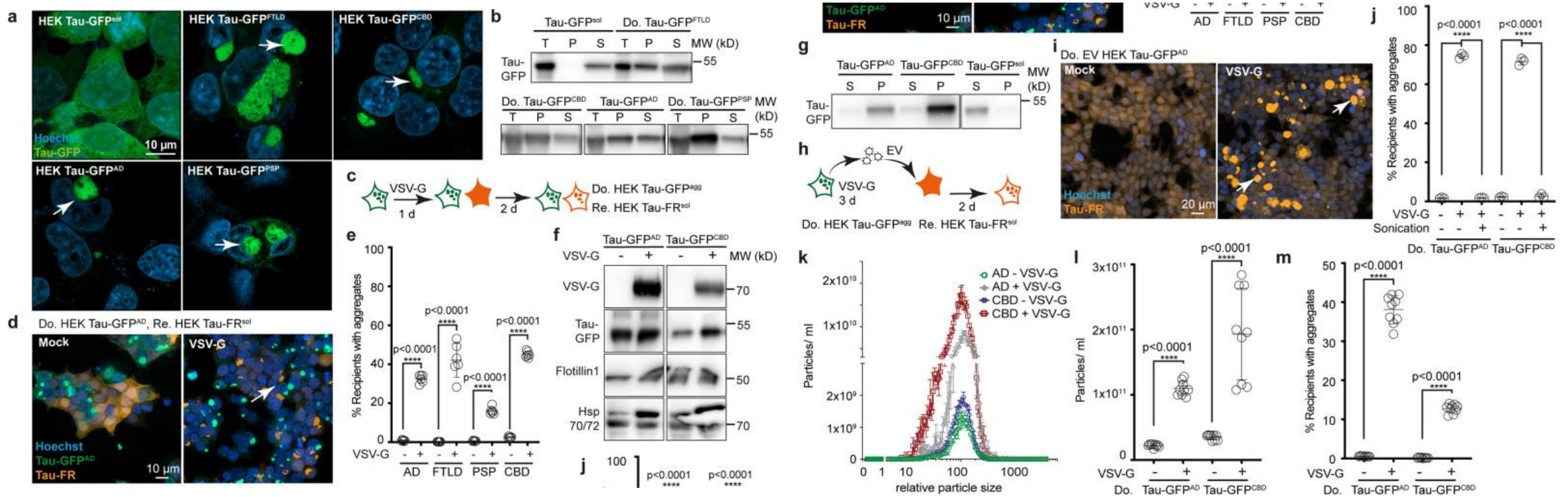
Baf: 内酸化H+ATP酶抑制剂
 CQ: 提高内吞体PH
 Dyn: 阻止网格蛋白内吞作用
 Api: pIKfyve抑制剂, 抑制溶酶体成熟



4. Enhanced intercellular transmission of Tau aggregation upon VSV-G expression



Fig 4

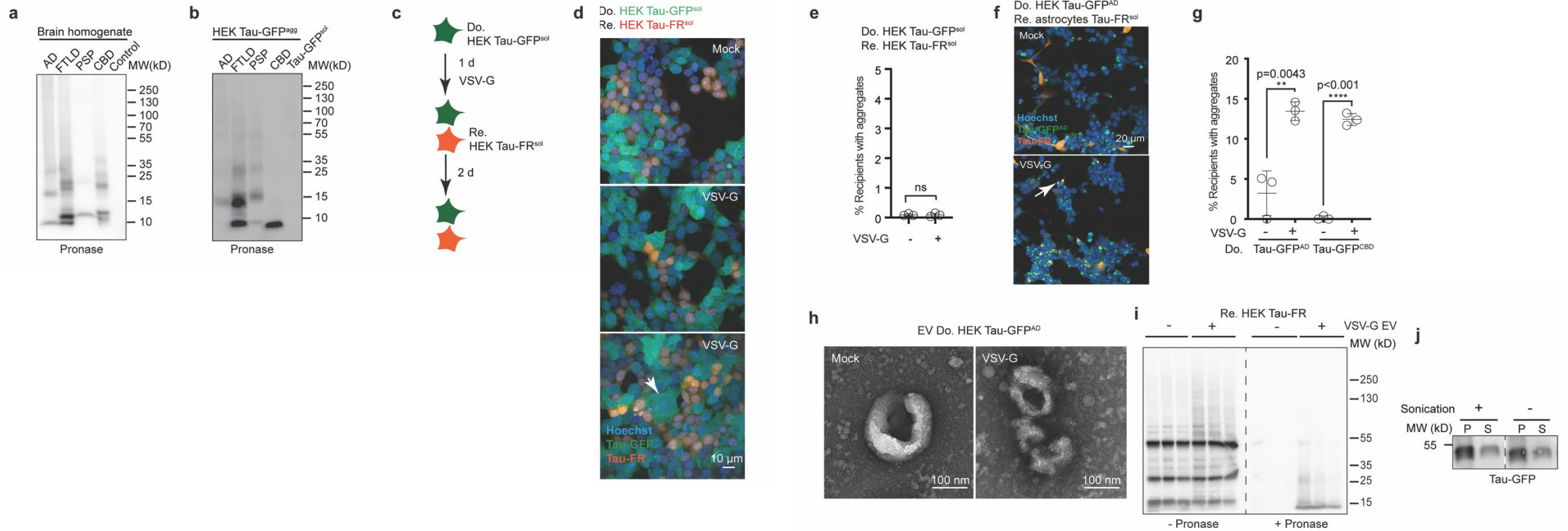




4. Enhanced intercellular transmission of Tau aggregation upon VSV-G expression



Suppl. figure 5

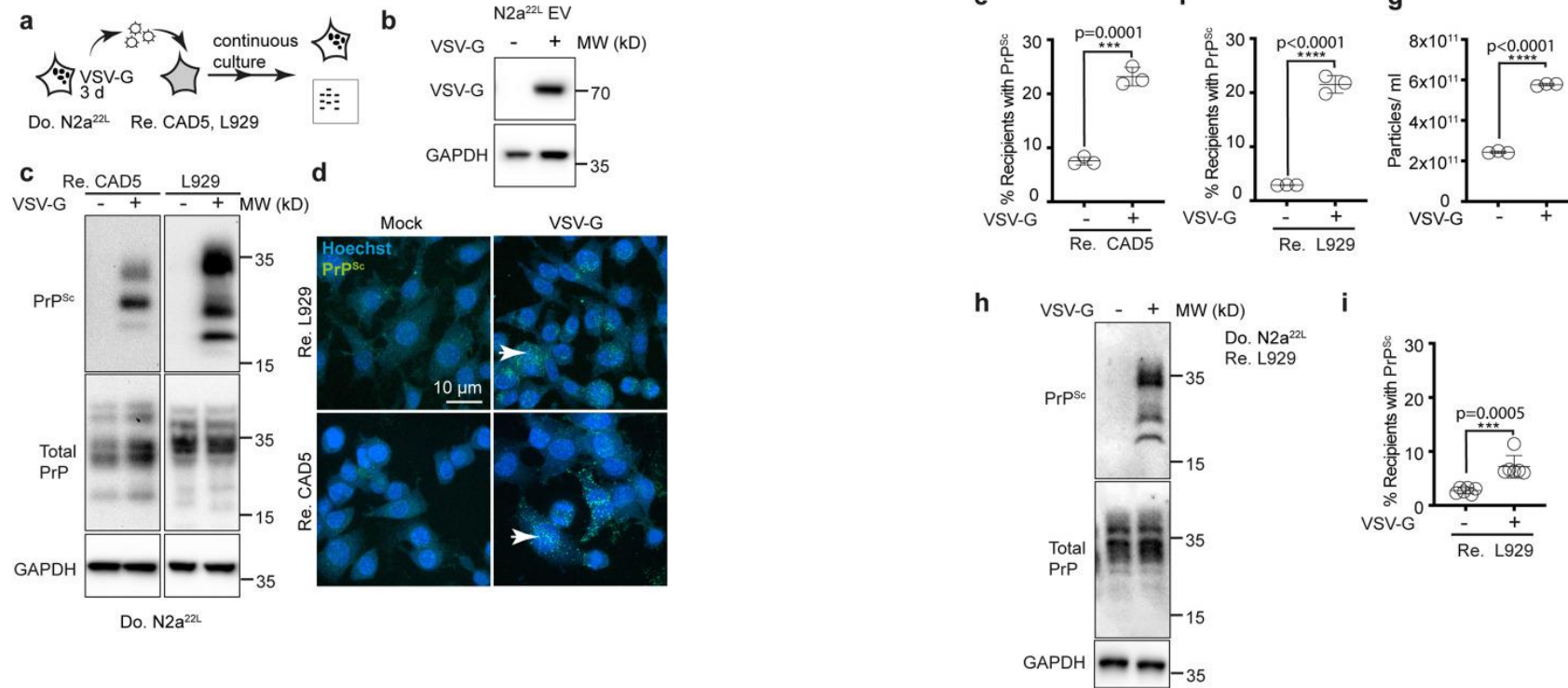




5. VSV-G-pseudotyped EV efficiently transmit scrapie prions to recipient cells



Fig 5



PrP^C是一种细胞朊病毒蛋白，通过碳基磷脂酰锚定在细胞膜上。可以转化为聚集亚型PrP^{Sc}。



6. Increased proteopathic seed spreading upon SARS-CoV-2 spike S expression.



Fig 6

