Table 2. Summary of model validation. The phenotypical behavior of the model is compared to gene expression datasets, laboratory experiments, and previous literature.

Associated Behavior	Model-Based Phenotypical Description (Attractor)	Validation	
		Literature	Wet Lab/Dataset Analyses
Overexpression of active CFL1	PRKD1 (inactive)	[130,131]	
	TCF7L2 (active)		GSE15471, GSE16515, GSE32676 (see Figure 4b)
	AURKA (active)		GSE15471, GSE16515, GSE32676 (see Figure 4a)
	SSH1L (active)	[61]	
Invasion	KRAS (active)	[3,46,78,79]	
	RAC1 (active)	[132]	
	ARP 2/3 (active)	[133,134]	
	F-actin$_{new}$ (active)	[135,136]	Time lapse Figure 2b
Proliferation	STAT3 (active)		Western blot Figure 4d
	AKT (active)	[137,138]	
	MYC (active)		Western blot Figure 4d
	CCND1 (active)		Western blot Figure 4d
Survival	AKT (active)	[137,138]	
	STAT3 (active)		Western blot Figure 4d
	Anti-apoptotic proteins (active)		GSE15471, GSE16515, GSE32676 (see Figure 4e)
	Caspases (inactive)		Western blot Figure 2a

3.6. Ras-Induced Imbalance in Actin Remodeling Leads to Overexpressed and Activated CFL1

First, we concentrated on processes leading to overexpression and activation of CFL1. Following the progression towards cancer, our model shows an imbalance between the two opponents ras homolog family member A (RHOA) and ras-related botulinum toxin substrate 1 (RAC1) in favor of RAC1 (Figure 3b). Thus, protein kinase D1 (PRKD1) downstream of RHOA is rendered inactive and enables the expression of TCF7L2, an inducer of CFL1 expression. On the other hand, by acting on p21 activating kinase 1 (PAK1), RAC1 activates aurora kinase A (AURKA). AURKA phosphorylates and thus activates slingshot-1L (SSH1L), one of the activators of CFL1. Based on the network evolution over time, we assume that an imbalance in actin remodeling induced by KRAS acting on PI3K results in overexpression and activation of CFL1.

Our mechanistic hypothesis is supported by gene expression data, showing that both AURKA and TCF7L2 are significantly overexpressed in pancreatic tumor tissues in comparison to healthy donors (Figure 4a,b). Here, binarization of the expression data classified tumor samples as active in contrast to healthy samples. As a further support, results were compared to literature findings (Table 2).