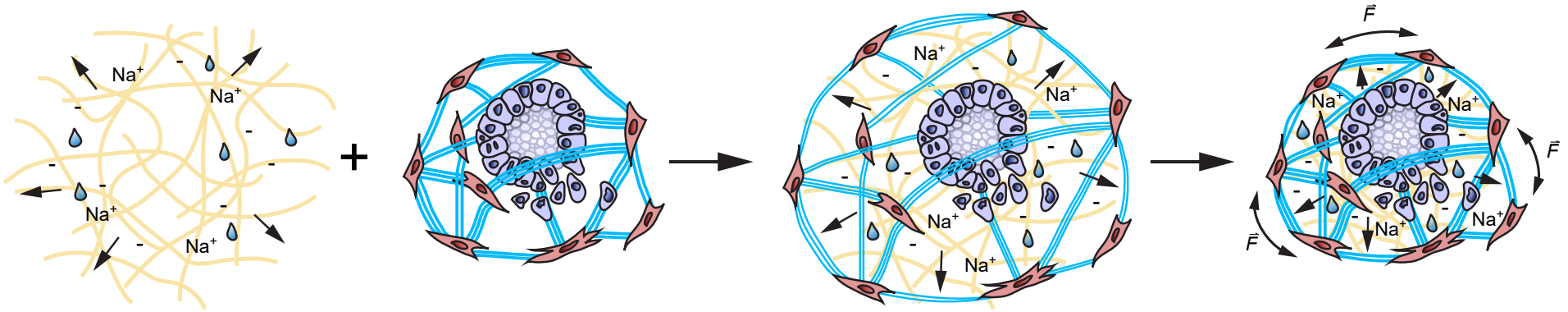
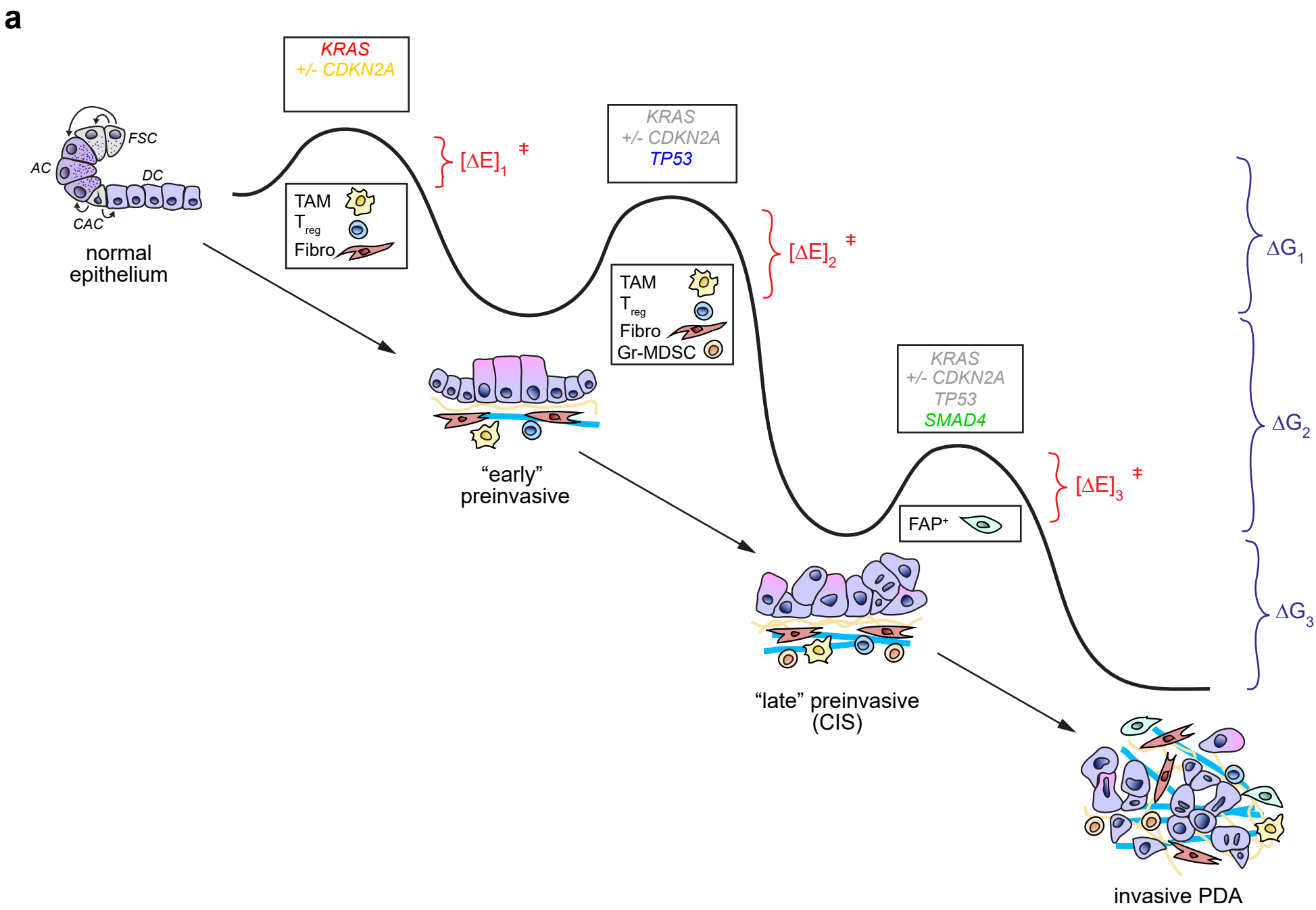


Supplementary Fig. 1 | Interstitial pressures generated by the stroma in pancreas cancer. High molecular weight (i.e. megadalton) hyaluronan binds water through multiple mechanisms with varying degrees of avidity. Both physical and chemical interactions (including the Donnan effect) enable HMW HA to imbibe large amounts of water to create a poorly mobile fluid phase. Pressures applied to, and generated by, this gel-fluid phase are therefore transmitted hydraulically (i.e. uniformly in all directions across the medium). The binding energy of complexed water (i.e. the decrease in chemical potential of water in the bound state), together with the highly negatively charged structure, contributes to the generation of enormous swelling pressures. Non-covalent interactions ("entanglement") between the hydrated HA strands and cell-bound collagen fibrils enable the expanding gel-fluid phase to load those fibrils and, in turn, stimulate a contractile response by the attached cells in their attempt to maintain tensional homeostasis. This equipoise between countervailing forces generates extraordinary interstitial pressures that are transmitted across the tumor bed, albeit at considerable metabolic expense. Enormous energy input (in the form of ATP) is required to maintain the actomyosin contractile machinery in an activated state.


a
KRAS
+/- CDKN2A
FSC
AC
DC
CAC
normal
epithelium
TAM
T reg
Fibro
[ΔE]1 ‡
KRAS
+/- CDKN2A
TP53
TAM
T reg
Fibro
Gr-MDSC
[ΔE]2 ‡
"early"
preinvasive
KRAS
+/- CDKN2A
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SMAD4
FAP+
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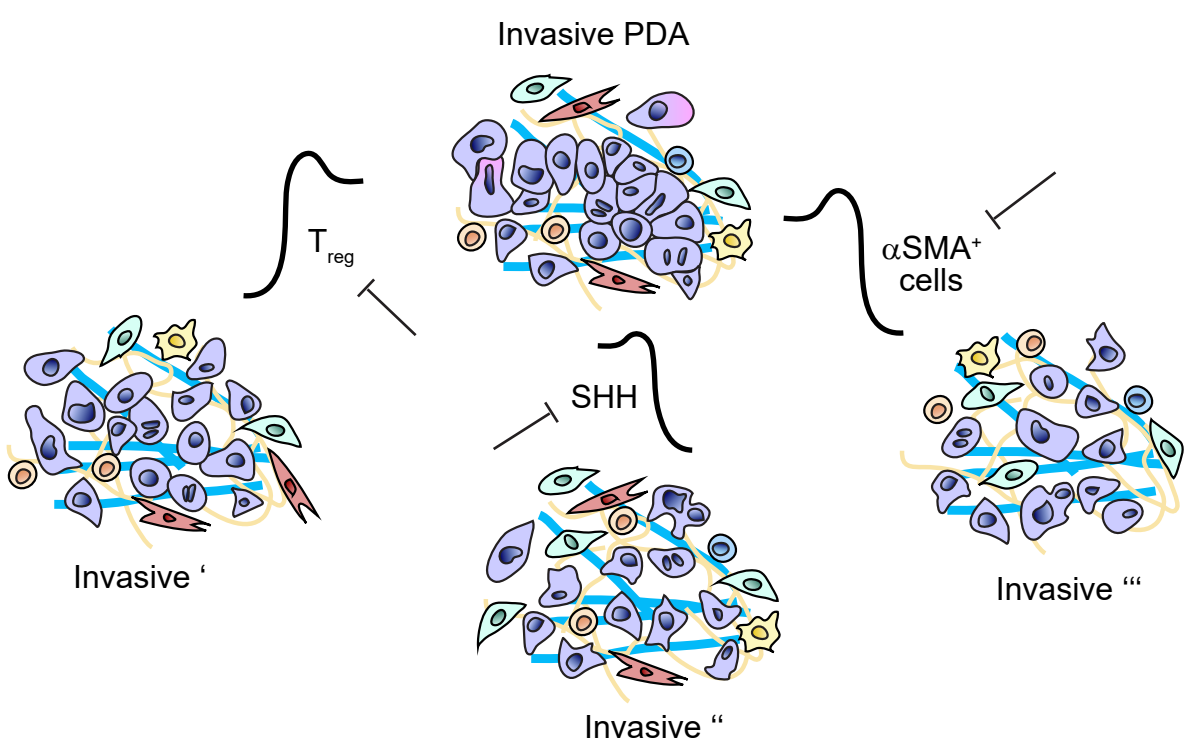
"late" preinvasive
(CIS)
invasive PDA
ΔG1
ΔG2
ΔG3



Supplementary Fig. 2 | Integrated epithelial and stromal progression models for pancreas cancer and thermodynamic implications. **a,** Cell autonomous (genetic) and non-cell autonomous (non-malignant cells and matrix components) events and processes cooperate in pancreatic carcinogenesis. The progression model can be conceptualized as a series of semi-stable states with sequentially lower free energy (i.e. increased entropy or dedifferentiation). The states are separated by transition states that represent energy barriers or constraints to transformation. Specific cell autonomous events and non-cell autonomous events and processes are required to surmount each of these barriers to tumorigenesis as revealed by their temporal occurrence in the progression scheme. Those events most critical to surmounting the transition state and/or maintaining the integrity of a given stage would represent the most attractive targets therapeutically. AC, acinar cell; DC, ductal cell; CAC, centroacinar cell; FSC, facultative stem cell; CIS, carcinoma-in-situ. **b,** Targeting a critical element(s) of the organizational logic of the pancreas cancer neo-organ may be catastrophic or may instead only transiently disrupt the relative homeostasis of the tumor. The tumor may then recover by reestablishing an even less ordered, more aggressive disease biology. As examples, sustained Hh inhibition, T_{reg} depletion, and ablation of αSMA-expressing cells have each been shown to dramatically affect the composition, architecture, and pathophysiology of the disease, only to see the emergence of a more lethal state. In the case of sustained Hh inhibition, a more aggressive, undifferentiated disease emerged with greater metastatic potential than at presentation; this was also accompanied, however, by a newly manifested angiogenesis, creating a potential vulnerability that was not present prior to treatment. Similarly, depletion of αSMA+ cells produced a more aggressive disease, characterized by an influx of T_{reg} but also increased checkpoint activation in CD8+ T cells and, therefore, a newfound sensitivity to checkpoint inhibition. The same principles underlie the typical emergence of a more poorly differentiated cancer after multiple cycles of conventional chemotherapy. Thus, an applied therapy or therapies may have little to no effect on a subtype-specific PDA; it may disrupt the internal logic sufficiently to induce a catastrophic event, potentially undoing the tumor; or, it may force it into a new, lower energy, less well-organized – and therefore more aggressive – state.