Supplementary Information

Supplementary Methods

Calculation of relative Erk activity wave peak amplitude

The relative Erk activity peak after treatment was calculated as

\[ \text{ErkAct}_{\text{rel}} = \frac{\text{ErkAct}_{\text{after}} - \text{ErkAct}_{\text{min}}}{\text{ErkAct}_{\text{before}} - \text{ErkAct}_{\text{min}}} \]

where \( \text{ErkAct} \) is the ratio of ErkKTR in the cytoplasmic to nuclear compartment, and \( \text{ErkAct}_{\text{min}} \) is the lower bound of ErkAct, calculated as the \( \sim 10\% \) percentile of ErkAct before treatment.

Mathematical model of Erk activity propagation – Equations and parameters

\[
\frac{dE}{dt} = \frac{\alpha_1 A^2}{\beta_1^2 + A^2} (1 - E) - E(\gamma_1 I + \gamma_e)
\]

\[
\frac{\partial A}{\partial t} = \alpha_2 + \alpha_3 E - \gamma_2 A + D \nabla^2 A
\]

\[
\frac{dI}{dt} = \gamma_3 (\alpha_4 E - I)
\]

where \( \alpha_1 \) is the Erk activation rate at saturating activator, \( \beta_1 \) is the AC_{50} of Erk activation by the activator, \( \gamma_1 \) is the Erk inactivation rate by the inhibitor I, \( \gamma_e \) is the Erk autonomous deactivation rate, \( \alpha_2 \) is the activator production rate in the source region, \( \alpha_3 \) is the Erk-dependent activator production rate, \( \gamma_2 \) is the autonomous activator decay rate, \( \gamma_3 \alpha_4 \) is the inhibitor production rate and \( \gamma_3 \) is the inhibitor autonomous degradation rate.

The parameters for the standard simulation of Fig. 3b and Extended Data Fig. 6a are:

\( \alpha_1: 7.2 \, \text{h}^{-1}, \beta_1: 0.35, \gamma_1: 8.8 \, \text{h}^{-1}, \gamma_e: 0.08 \, \text{h}^{-1}, \alpha_2: 0.06 \, \text{h}^{-1} \) in the source region (null outside), \( \alpha_3: 2.2 \, \text{h}^{-1}, \gamma_2: 6.9 \, \text{h}^{-1}, D: 432 \, \mu\text{m}^2/\text{h}, \gamma_3: 0.08 \, \text{h}^{-1} \) and \( \alpha_4: 0.5 \). The same parameters are used for the ablation simulation (phase and trigger wave, Fig. 3c, d), except that the source region production rate \( \alpha_2 \) is set to zero after 30 h to prevent the formation of a second wave. For Fig. 3e, the standard set of parameters is used, while Mek inhibition is implemented by reducing the value of \( \alpha_1 \).
Wave velocity corrected for tissue growth calculation

Corrected velocity was calculated as:

\[ v_{\text{corrected}} = \frac{1}{\Delta t} \left( X(t + \Delta t)_{\text{wave}} \frac{X(t)_{\text{border}}}{X(t + \Delta t)_{\text{border}}} - X(t)_{\text{wave}} \right), \]

where \( v_{\text{corrected}} \) is the corrected wave velocity, \( \Delta t \) is the time-interval between two time-points and \( X(t)_{\text{border}} \) and \( X(t)_{\text{wave}} \) are, respectively, the position of the external scale border rim and of the wave.

Supplementary Notes

Effects of Fgfr pharmacological and genetic perturbations

We tested the effects of several Fgf receptor perturbations on Erk waves. We found that treatment with the pan-Fgfr inhibitor BGJ398 or JNJ-42756493 ablates Erk waves (Extended Data Fig. 3a-e) and that BGJ398 affects waves within a few hours (Extended Data Fig. 3c). Treatment with the Fgfr inhibitor SU5402 partially impairs waves on a time-scale of 12 h; then, Erk waves peaks return to basal level 24 h after the start of treatment (Extended Data Fig. 3f, g).

Heat-shocked expression of a \textit{dnfgfr1} transgene, a dominant negative version of the Fgfr1, partially inhibits scale growth (Extended Data Fig. 2b) and partially impairs Erk waves on the time-scale of 10 h (Extended Data Fig. 4a, b). To further test the effects of expression of \textit{dnfgfr1} on Erk activity, we measured the expression of \textit{spry4} transcript in \textit{hsp70l:dnfgfr1} scales (\textit{spry4} levels correlate with Erk activity and are suppressed by Erk inhibition - see below; Extended Data Fig. 5h-i). We found that \textit{spry4} transcripts are reduced in scales in which \textit{dnfgfr1} was expressed (Extended Data Fig. 5j).

Together with the observation that over-expression of Fgf ligands is sufficient to activate Erk (Extended Data Fig. 4c-f), these results suggest that Erk waves are at least partially
dependent on Fgfr signalling. We do not exclude the involvement of other signals in the generation and propagation of Erk waves.

**Venus-hGeminin degradation is patterned in the hypertrophic phase of scale regeneration** The proposed model of Erk trigger waves propagation predicts that Erk-active cells activate one or more inhibitors that reduce Erk activity with a delay (see main text). Erk-responsive antagonists such as dual-specificity phosphatases (Dusp) and Sprouty proteins could provide a mechanism of Erk inhibition\(^1\). To examine this idea, we developed a sorting strategy to collect two osteoblast populations from regenerating scales: one enriched for cells with low Erk activity (Erk-) and one enriched for cells with high Erk activity (Erk+). We describe here the procedure we applied to sort the two populations of osteoblasts and test for the differential expression of Erk-antagonist genes.

The Erk activity measurement of ErkKTR-mCerulean is based on differential subcellular sensor localization, and not its intensity. Therefore, it is likely difficult to sort Erk+ and Erk- osteoblasts by flow cytometry using ErkKTR-mCerulean. However, we found that another transgenic sensor, i.e. the Cdh1 sensor Venus-hGemini\(^2\), is patterned in disk/ring shapes and excluded from Erk active regions in osteoblasts during the hypertrophic phase of scale regeneration (Extended Data Fig. 5a, b). *osx:*Venus-hGemini\(^2\), together with *osx:*mCherry-zCdt1\(^2\), form a Fluorescence Ubiquitination Cell Cycle Indicator\(^3\) (FUCCI), originally developed to distinguish cells in G1/G0 (Venus-hGeminin\(^-\) and mCherry-zCdt1\(^+\)) and S/G2/M (Venus-hGeminin\(^+\) and mCherry-zCdt1\(^-\)) based on the cell-cycle dependent ubiquitination and degradation of the cell cycle oscillator-derived proteins hGeminin and zCdt1. Although central osteoblasts do not incorporate EdU or proliferate during the hypertrophic phase of scale regeneration (Extended Data Fig. 1d-h), we observe hGeminin\(^+\) regions. To ascertain that those hGeminin\(^+\) osteoblasts are not in S/G2/M phases, we imaged
and measured Venus-hGeminin and mCherry-zCdt1 intensity in individual osteoblasts during the hypertrophic phase and compared them with those in the proliferative phase. As previously reported², during the proliferative phase, osteoblasts are divided in two populations of similar magnitude, one likely in G1/G0 phases (Venus-hGeminin⁺ and zCdt1⁻) and one likely in S/G2/M phase (Venus-hGeminin⁺ and mCherry-zCdt1⁻) (Extended Data Fig. 5c-e). Instead, we found that, during the hypertrophic phase, mCherry-zCdt1 intensity is consistently high in osteoblast, including in cells having high levels of Venus-hGeminin (Extended Data Fig. 5c-e). This is compatible with the notion that those osteoblasts are in G1/G0 phase, as Cdt1 degradation is needed for entry in S phase. In conclusion, we found a population of poorly or non-proliferative cells in which Venus-hGeminin is stabilized, potentially indicating cell-cycle-independent inactivation of the Cdh1 complex.

**Sorting strategy for Erk-active osteoblasts, and selected sequencing results**

Regardless of the molecular details underlying the stabilization of Venus-hGeminin, we observed that Venus-hGeminin⁺ regions are organized in rings excluded from Erk active regions (Extended Data Fig. 5a). To test this observation quantitatively, we tracked Venus-hGeminin intensity and Erk activity at the same time in individual osteoblast over the course of ~3 days (Extended Data Fig. 5b). We found that Venus-hGeminin peak is achieved when Erk activity is low and vice versa. Thus, we reasoned that by sorting cells on the basis of the osx:H2A-mCherry osteoblast marker (to enrich for osteoblasts over other cell types) and on the basis of the intensities of Venus-hGeminin, we could obtain two populations, one enriched in Erk-active osteoblasts (osx:H2A-mCherry⁺; osx:Venus-hGeminin⁻) and one enriched in Erk-inactive osteoblasts (osx:H2A-mCherry⁺; osx:Venus-hGeminin⁺).

Thus, we plucked regenerating scales at 4 dpp, dissociated cells and applied this strategy to obtain Erk⁺ and Erk⁻ osteoblast populations for RNA extraction and sequencing.
(Extended Data Fig. 5f). We found that MAPK signalling pathway activation is increased in the Erk+ population compared with the Erk- population, confirming the validity of the sorting strategy (Extended Data Fig. 5g). We focused on dual-phosphatases (dusp) that are specifically reported to inhibit Erk and sprouty genes1,4, and found that several dusp and spry genes are expressed in scale osteoblasts. Notably, dusp2, dusp5 and spry4 are enriched in Erk+ cells (Extended Data Fig. 5h). We further tested the role of Erk in promoting the expression of dusp2, dusp5 and spry4 by measuring using real-time qPCR their expression in whole scales in which Erk was inhibited by treatment with the Mek inhibitor PD0325901. We found that dusp5 and spry4 transcripts were reduced compared with control, while effects on dusp2 were variable (Extended Data Fig. 5i).

We also noticed that the heparan sulfate proteoglycan syndecan 4 (sdc4), a regulator of Fgf diffusion and signalling5, is enriched in Erk+ osteoblasts, consistent with activation of a Fgf regulatory mechanism in those cells (Extended Data Fig. 5h). Finally, activation of bone morphogenesis pathways is increased in the Erk+ population compared with the Erk- population (Extended Data Fig. 5g, Supplementary Table 1).

**Trigger waves versus signal propagation by simple diffusion**

Our quantitative analysis of trigger waves estimated the effective diffusion constant of the Erk activator to be $D \approx 0.1 \mu\text{m}^2 \text{s}^{-1}$. With this diffusion constant of the activator, in our model Erk waves cross a millimetre-sized tissue in just a few days (Extended Data Fig. 6g). This is different from a model in which the activator spreads by simple diffusion, as in the morphogen gradient model. In this second case, with diffusion constant of $0.1 \mu\text{m}^2 \text{s}^{-1}$, the activator would travel rapidly across distances on the order of 10–50 µm, as in the *Drosophila* wing disc or mouse neural tube6,7, but it would require weeks to cross a millimetre-wide adult zebrafish scale (Extended Data Fig. 6g). While the geometrical properties of Erk waves argue for a low
value of the diffusion constant (Fig. 2f, 3g, Extended Data Fig. 6f), the measured diffusion constants of signalling molecules (e.g. Fgfs) are context-dependent\textsuperscript{5,8-10} and can span several orders of magnitude, the highest of which would be compatible with their spreading across the osteoblast tissue on the timescale of regeneration.

**Minimal mechanical model of tissue growth**

Our experiments indicate that Erk waves, propagating as trigger waves across the osteoblast population during the hypertrophic phase, instruct localized tissue growth. Furthermore, we observe that tissue-wide Erk activation, induced by over-expression of two different Fgfs, reduces tissue growth with respect to baseline wave-like Erk activation. A possible interpretation of this phenomenon is that Erk activation over a broad spatial range causes synchronous and broad-range tissue growth, which in turn leads to build up of mechanical stress (pressure). As mechanical stress is an emerging regulator of cell growth\textsuperscript{11-13}, this potential excess pressure would stunt growth and lead to reduced overall scale size. Here, we develop a simplified 1D mechanical model of tissue growth to illustrate this model quantitatively.

**Tissue mechanics**

We describe the tissue as 1D continuous material of length $L(t)$ and density $\rho(x,t)$ where $0 < x < L$ is the spatial coordinate and $t$ is the temporal coordinate. Following Ref.\textsuperscript{12}, we assume that internal pressure increases linearly with density as

$$p(x,t) = p_0 + \frac{1}{\chi}(\rho(x) - \rho_0)$$

(1)

where $p_0$ and $\rho_0$ are, respectively, the equilibrium pressure and density in the absence of growth (see below).
Over the time-scale of growth, the tissue behaves as a viscous fluid of effective viscosity $\eta$ (see Refs.\textsuperscript{12,13}). In addition, tissue movements are subject to friction (friction coefficient $\gamma$) against neighbouring structures, such as the bone or the extra-cellular matrix. Thus, stress is:

$$\sigma(x) = \eta \frac{\partial v}{\partial x} - p(x)$$

and, assuming that elastic equilibrium is reached on a shorter time-scale than tissue growth

$$\frac{\partial \sigma}{\partial x} = \gamma v$$

Thus,

$$\eta \frac{\partial^2 v}{\partial x^2} - \gamma v = \frac{1}{\chi} \frac{\partial \rho}{\partial x}$$

We assume that the anterior side of the scale is limited in its movement by the dermal pocket. For the posterior edge, we assume that the stress is equal to an external pressure, which for sake of simplicity we choose to be equal to $p_0$, that is the pressure of the tissue at rest. Thus, we obtain the boundary conditions:

$$v(0) = 0$$

$$\sigma(L) = -p_0$$

From (6) we can derive a boundary condition for the velocity:

$$\left. \frac{\partial v}{\partial x} \right|_{x=L} = \frac{1}{\eta \chi} \left( \rho(L) - \rho_0 \right)$$

_Tissue growth_

Tissue density changes with the mass-balance equation

$$\frac{\partial \rho}{\partial t} + \frac{\partial (\rho v)}{\partial x} = k(x,t)$$

where $k(x,t)$ is local tissue growth. Following Ref.\textsuperscript{12}, we assume that growth depends linearly on pressure, so that
\[ k(x, t) = \max (k_0(x, t) \left( 1 - \frac{\rho(x) - \rho_0}{\rho_{\text{max}} - \rho_0} \right), 0) \]

where \( k_0(x, t) \) is the basal rate of growth in absence of pressure build-up, that is the one when \( \rho = \rho_0 \). We assume that Erk waves trigger growth. Thus, we introduce a basal rate of growth that travels as a wave:

\[ k_0(x, t) = k_0^{\text{peak}} \frac{1}{\sqrt{2\pi\sigma(t)}} e^{-\frac{(x-\mu(t))^2}{2\sigma(t)^2}} \]

where \( \mu(t) = v_{\text{wave}} \frac{L(t)}{L(0)} \) is the position of the growth peak and \( \sigma(t) = \sigma_0 \frac{L(t)}{L(0)} \) is its width.

The modelled wave position and width are distorted by tissue growth, but similar conclusions are obtained if the basal growth wave is not affected by tissue growth. In the case of spatially broad Erk activation, we impose a uniform basal rate of growth equal to that of a cell in the centre of the domain (equivalent to transforming a traveling wave into uniform oscillators with identical single cell dynamics):

\[ k_0(x, t) = k_0^{\text{peak}} \frac{1}{\sqrt{2\pi\sigma(t)}} e^{-\frac{(L/2 - \mu(t))^2}{2\sigma(t)^2}} \]

We solve the coupled equations (4) and (8) numerically using a finite differences method (an implementation of the MacCormack method\(^{14}\)). As these equations have a moving boundary at \( x = L \), the variable \( \xi = \frac{x}{L} \) is introduced, equations are rescaled and the system is solved using a fixed discretization of \( \xi \) and \( t \).

As proof of principle, we show in Extended Data Fig. 10 two simulations for parameters in the frictional regime, one with wave-like basal growth (Extended Data Fig. 10a, c) and one with uniform basal growth (Extended Data Fig. 10b). In the case of uniform basal growth, excess pressure accumulates in the tissue, leading to reduced tissue expansion \( \frac{\partial \rho}{\partial x} \). As a result, uniform basal growth leads to a smaller final tissue size compared with wave-like basal growth.
(Extended Data Fig. 10d), as observed in the experiments over-expressing Fgf ligands (Figure 4f, Extended Data Fig. 8-9).

Properties of tissue flows

Tissue flows described by (4) are characterized by the correlation length \( l = \frac{\sqrt{\pi}}{\gamma} \) and \( \frac{\partial v}{\partial x} \) is the rate of local tissue expansion. Our model suggests that the scale tissue may operate in the frictional regime, in which Erk waves are favourable to uniform Erk activation for scale growth. To test whether the regenerating scale tissue operates indeed in the friction regime, we measured the two-point correlation function of the tissue velocity field (Extended Data Figure 10e). This function is well approximated by an exponential decay with a length scale \( l \sim 100 \mu m \), thus much smaller than the dimension of the system \( \frac{l}{L} \sim 0.1 \), arguing in favor of the frictional regime. In this frictional regime, \( \gamma v \approx -\frac{1}{\chi} \frac{\partial \rho}{\partial x} \) and thus we expect the vorticity \( \omega = \nabla \times v \) to vanish. Quantification of the tissue flow vorticity indicated that it is in the order of 0.001 h\(^{-1}\) (Extended Data Fig. 10f and its legend), which has to be compared with the typical scale \( v/\lambda_{\text{vorticity}} \), where \( v \sim 0.5 \mu m \) h\(^{-1}\) is the average flow velocity (see legend Extended Data Fig. 10f) and the correlation length-scale of the vorticity field is \( \lambda \sim 30 \mu m \) (Extended Data Figure 10g). Therefore, tissue flow vorticity is an order of magnitude smaller compared to \( v/\lambda \), as expected in the frictional regime (Extended Data Figure 10h).

Importantly, in the viscous regime \((l \gg L)\), increases in density cannot lead to the formation of compression regions, that is regions in which \( \frac{\partial v}{\partial x} < 0 \), as in that regime \( \frac{\partial v}{\partial x} \approx \frac{\rho(x) - \rho_0}{\eta \chi} \). Instead, compression regions are observed in our experiments. On the contrary, in the frictional regime tissue compression can be generated where density concavity is positive and the term \( \frac{\eta}{\gamma \chi} \frac{\partial^2 v}{\partial x^2} \) can be neglected, as in those regions \( \frac{\partial v}{\partial x} \approx -\frac{1}{\gamma \chi} \frac{\partial^2 \rho}{\partial x^2} \). Thus, in the approximation...
in which tissue density correlates with Erk activity, the position of the region of compression can be determined by the concavity of the Erk profile. Indeed, we confirmed experimentally that tissue compression troughs are predicted by peaks of Erk concavity (Extended Data Fig. 10i).

Our analysis indicates that scale flows are compatible with the predictions from the frictional regime. Moreover, the velocity field is essentially irrotational, implicating that it can be described as the gradient of an effective pressure field, as in Eq. (4).

Another geometric feature observed following ectopic expression of Fgf ligands is compatible with our model. Given the different boundary conditions at the anterior and the posterior of the scale, we expect that, following long-range Erk activation pressure build-up will lead to flows biased toward the scale posterior (Extended Data Figure 10j). Whereas following the first heat-shock the average flow direction is variable, after the second heat-shock it orients toward the posterior. We reasoned that this may be due to variable initial conditions at the time of the first heat-shock. Thus, we performed an experiment in which ectopic expression of the \textit{fgf20a} ligand gene was performed following pharmacological inhibition of Erk for 24 hours by PD0325901 treatment. After heat-shock, fish were returned to the pharmacological treatment. In this case, given the more uniform initial conditions, we expect cellular flows to be more biased toward the posterior, which was confirmed experimentally (Extended Data Figure 10j-l). Collectively, our model captures several aspects of Erk-induced tissue growth.

In the future, it will be interesting to further test this model by generating tools to modulate Erk activity in specific scale regions and to measure the consequent mechanical changes in the affected tissue.

\textit{Mechanical model parameters}
\(L(0) = 0.5\) mm, \(\rho_0 = 10^5\) mm\(^3\), \(k_0\text{peak} = 0.1\rho_0\), \(\rho_{\text{max}} = 0.25\rho_0\), \(v_{\text{wave}} = 0.5\ L(0)\ \text{d}^{-1}\), \(\sigma_0 = 0.04\ L(0)\). \(\chi = 10^{-3}\ \rho_0\) Pa is chosen according to Ref. \(^{12}\). The correlation length \(l = 0.1\ L(0)\) is chosen in the frictional regime. \(\gamma = 4.10^3\ \text{Pa d mm}^2\) is chosen such that the half-time to reach equilibrium length for a tissue with a density peak of \(0.1\ \rho_0\) is in the order of 5 h. In the frictional regime, similar effects can be obtained varying \(\gamma\) and \(\rho_{\text{max}}\) within two orders of magnitude.

**Initial scale areas and average cell areas in perturbation experiments. Mean with SEM.**

Fig 4f. Area before heat-shock: control \(\text{hsp70l:mCherry-2a-fgf20a siblings}\) (3.6 \(\pm\) 0.3) \(10^5\ \mu\text{m}^2\); \(\text{hsp70l:mCherry-2a-fgf20a}\) (4.6 \(\pm\) 0.5) \(10^5\ \mu\text{m}^2\); control \(\text{hsp70l:fgf3 siblings}\) (4.3 \(\pm\) 0.4) \(10^5\ \mu\text{m}^2\); \(\text{hsp70l:fgf3}\) (3.8 \(\pm\) 0.2) \(10^5\ \mu\text{m}^2\).

Extended Data Fig. 2a. Area before treatment: DMSO (4.6 \(\pm\) 0.5) \(10^5\ \mu\text{m}^2\); PD0325901 (4.3 \(\pm\) 0.4) \(10^5\ \mu\text{m}^2\). Cell area before treatment: control DMSO (148 \(\pm\) 4) \(\mu\text{m}^2\); PD0325901 (157 \(\pm\) 6) \(\mu\text{m}^2\).

Extended Data Fig. 2b. Average area before heat-shock: control siblings (5.4 \(\pm\) 0.3) \(10^5\ \mu\text{m}^2\); \(\text{hsp70l:dnfgfr1-EGFP}\) (4.4 \(\pm\) 0.3) \(10^5\ \mu\text{m}^2\). Average cell area before heat-shock (with SEM): control siblings (171 \(\pm\) 3) \(\mu\text{m}^2\); \(\text{hsp70:dnfgfr1-EGFP}\) (164 \(\pm\) 5) \(\mu\text{m}^2\).

Extended Data Fig. 8e. Average cell area before first heat-shock: control sibling (150 \(\pm\) 10) \(\mu\text{m}^2\); \(\text{hsp70l:mCherry-2a-fgf20a}\) (134 \(\pm\) 3) \(\mu\text{m}^2\).

Extended Data Fig. 9c. Average cell area before first heat-shock: control sibling (153 \(\pm\) 4) \(\mu\text{m}^2\); \(\text{hsp70l:fgf3}\) (150 \(\pm\) 4) \(\mu\text{m}^2\).
Supplementary References

1. Lake, D., Correa, S. A. & Muller, J. Negative feedback regulation of the ERK1/2 MAPK pathway. *Cell Mol Life Sci* **73**, 4397-4413, doi:10.1007/s00018-016-2297-8 (2016).

2. Cox, B. D. *et al.* In Toto Imaging of Dynamic Osteoblast Behaviors in Regenerating Skeletal Bone. *Curr Biol* **28**, 3937-3947 e3934, doi:10.1016/j.cub.2018.10.052 (2018).

3. Sakaue-Sawano, A. *et al.* Visualizing spatiotemporal dynamics of multicellular cell-cycle progression. *Cell* **132**, 487-498, doi:10.1016/j.cell.2007.12.033 (2008).

4. Kidger, A. M. & Keyse, S. M. The regulation of oncogenic Ras/ERK signalling by dual-specificity mitogen activated protein kinase phosphatases (MKPs). *Semin Cell Dev Biol* **50**, 125-132, doi:10.1016/j.semcdb.2016.01.009 (2016).

5. Venero Galanternik, M., Kramer, K. L. & Piotrowski, T. Heparan Sulfate Proteoglycans Regulate Fgf Signaling and Cell Polarity during Collective Cell Migration. *Cell Rep* **10**, 414-428, doi:10.1016/j.celrep.2014.12.043 (2015).

6. Wartlick, O. *et al.* Dynamics of Dpp signaling and proliferation control. *Science* **331**, 1154-1159, doi:10.1126/science.1200037 (2011).

7. Zagorski, M. *et al.* Decoding of position in the developing neural tube from antiparallel morphogen gradients. *Science* **356**, 1379-1383, doi:10.1126/science.aam5887 (2017).

8. Yu, S. R. *et al.* Fgf8 morphogen gradient forms by a source-sink mechanism with freely diffusing molecules. *Nature* **461**, 533-536, doi:10.1038/nature08391 (2009).

9. Duchesne, L. *et al.* Transport of fibroblast growth factor 2 in the pericellular matrix is controlled by the spatial distribution of its binding sites in heparan sulfate. *PLoS Biol* **10**, e1001361, doi:10.1371/journal.pbio.1001361 (2012).

10. Muller, P., Rogers, K. W., Yu, S. R., Brand, M. & Schier, A. F. Morphogen transport. *Development* **140**, 1621-1638, doi:10.1242/dev.083519 (2013).
Shraiman, B. I. Mechanical feedback as a possible regulator of tissue growth. *Proc Natl Acad Sci U S A* **102**, 3318-3323, doi:10.1073/pnas.0404782102 (2005).

Basan, M., Risler, T., Joanny, J. F., Sastre-Garau, X. & Prost, J. Homeostatic competition drives tumor growth and metastasis nucleation. *HFSP J* **3**, 265-272, doi:10.2976/1.3086732 (2009).

Irvine, K. D. & Shraiman, B. I. Mechanical control of growth: ideas, facts and challenges. *Development* **144**, 4238-4248, doi:10.1242/dev.151902 (2017).

Griffiths, D. F. & Higham, D. J. MacCormack's method for advection-reaction equations. *Computational Fluid Dynamics Journal* **9** (2000).