



Flows of Research Manuscripts Among Scientific Journals Reveal Hidden Submission Patterns

V. Calcagno *et al.*
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(Fig. 1C). The agreement of data and synthetic stacks is a good indication of the quality of the retrieved Green's function.

We attribute the minor differences between field data and synthetics to structural differences between the global reference model (31) and Earth's mantle beneath the study area. To test this hypothesis, we calculated the synthetic seismogram stacks for a series of models (table S1), and we qualitatively evaluated the fit between the stack of synthetic seismograms and the correlations (fig. S3). With the AK135 model as reference, we modified the depths of the two discontinuities and used gradients over narrow depth intervals, rather than first-order discontinuities. The stack of synthetics associated with the best model (Fig. 2A) is in good agreement with the data: The overall fit of the observations was drastically improved relative to that obtained using the AK135 model. With this refined model, the arrival times and the relative *P410P* and *P660P* amplitudes are similar.

The final model (Fig. 2B) of our study shows a "410-km discontinuity" that is 15 km thick and ranges from 405 to 420 km in depth. The "660-km discontinuity" is 4 km thick, at depths of 650 to 654 km. The depths of these two discontinuities are within the variations observed at a global scale (4, 5) and are in good agreement with a receiver function study in the same area (32). Our additional constraints on the fine structure of the discontinuities corresponded to those predicted by the thermodynamic modeling of the phase transitions (33, 34) and to constraints provided by seismological studies (35, 36).

We have shown that it is possible to identify and characterize deep body waves that propagate through Earth. Our study used a dense seismic network that is located above a relatively transparent Earth crust. Using seismic noise to image mantle discontinuities has several advantages. First, the correlation technique is independent of earthquake occurrence, and therefore independent of the uncertainties that are associated with source location, origin time, and detailed slip history. Second, the amount of noise correlation scales according to N^2 , where N is the number of stations, so it is relatively easy to obtain a large amount of data. Finally, the body waves that we have extracted are relatively high frequency (0.1 to 0.5 Hz) and they are sufficiently broadband to finely resolve the structure of the discontinuities.

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Supplementary Materials

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Materials and Methods
Figs. S1 to S3
Table S1
Reference (37)

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Flows of Research Manuscripts Among Scientific Journals Reveal Hidden Submission Patterns

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The study of science-making is a growing discipline that builds largely on online publication and citation databases, while prepublication processes remain hidden. Here, we report on results from a large-scale survey of the submission process, covering 923 scientific journals from the biological sciences in years 2006 to 2008. Manuscript flows among journals revealed a modular submission network, with high-impact journals preferentially attracting submissions. However, about 75% of published articles were submitted first to the journal that would publish them, and high-impact journals published proportionally more articles that had been resubmitted from another journal. Submission history affected post-publication impact: Resubmissions from other journals received significantly more citations than first-intent submissions, and resubmissions between different journal communities received significantly fewer citations.

With the rise of Web technologies and online databases, knowledge is increasingly available regarding the process

of science-making itself (*J*). Gathering such "meta-knowledge" presents the opportunity to better understand, and optimize, the practice of research

(1, 2). Citation patterns have revealed research fronts (3), maps of science (4), and citation behavior (5, 6); coauthorship patterns have revealed

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collaboration networks (7); and even acknowledgments can help infer contributions to science-making (8). Yet all this research rests on the emerged part of science communication: publications. These represent only the outcome of a complex process that involves manuscript preparation, submission, peer review, and revision (9). Focusing on the final stage may give a very specific image of science (10, 11). Unfortunately, prepublication processes, which constitute a considerable amount of the time allocated to research, have remained a black box for which we lack systematic data (12–15).

To study prepublication history, we asked the corresponding author of virtually all research ar-

ticles published between 2006 and 2008 in 16 subject categories of biological sciences (923 journals) (table S1) whether the article was first submitted to the publishing journal and, if not, the name of the journal previously attempted (16). All evidence suggests that response bias was negligible (16). We thus retrieved the late submission history of 80,748 articles (37% of all enquiries), from which we could reconstruct the network of manuscript flows among scientific journals (Fig. 1 and fig. S2). In the network, an arrow from journal A to journal B represents a “resubmission link,” that is, an article that was submitted to and published by journal B after submission to journal

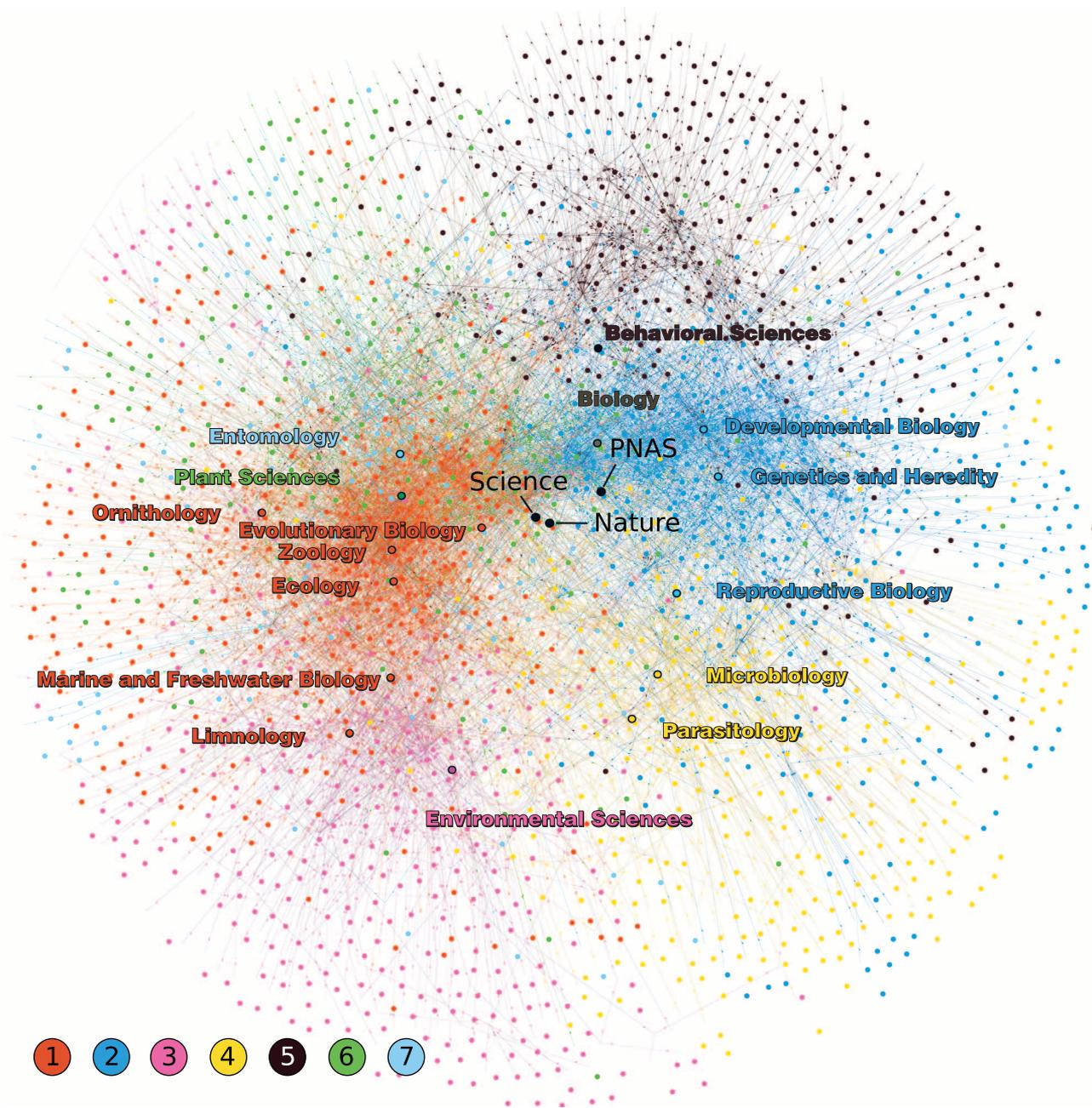


Fig. 1. The network of scientific journals as derived from manuscript submission flows. Nodes are journals, and the connections between them represent manuscript resubmissions (arrows not visible at this magnification level;

see fig. S2 for higher resolution). For clarity, only the seven largest communities detected ($N = 1841$ journals) are shown, each a different color. ISI subject categories are mapped on the graph as the centroid of their journals.

A. This network can be used to learn more about publication strategies and perceived journal importance than is available in citation networks alone (17, 18).

The submission network we obtained was densely connected (Fig. 1). Most journals are thus exchanging some manuscripts with at least one other journal (16 on average; first/third quartiles: 5/21). Resubmission flows were modular in that they occurred preferentially within subgroups of journals. Partitioning of the network with a modularity-maximizing algorithm (19) revealed seven principal communities (journal clusters). These were strongly consistent with subject categories as defined by the Institute for Scientific Information (ISI) (Fig. 1 and fig. S3), confirming the expectation that manuscript resubmissions should occur mainly within disciplines. The communities were less resolved than subject categories, though, and the resulting modularity value (0.5) was not extreme, indicating cross-community flow.

Journals more central in the resubmission network were also those with higher impact factor based on the ISI metric (Spearman correlation $\rho = 0.55$; $P < 0.001$) (fig. S4), especially the top three multidisciplinary journals included in our study (Fig. 1). Journal importance (20), here inferred from submission patterns, is thus associated with importance as inferred from citation patterns (17, 18). This could merely result from the fact that high-impact journals published more articles overall and so had more articles surveyed (fig. S4), which could increase centrality in itself.

We thus studied determinants of network centrality that are not affected by the number of articles published. The first quantity is the number

of times a journal was reported as an earlier choice for submission (the out-degree of a journal in the network). It increased sharply with impact factor (Fig. 2A) (Spearman rank correlation $\rho = 0.55$; $P < 0.001$), showing that high-impact-factor journals were more often earlier choices for submission. Furthermore, resubmission flows were highly nonreciprocal between pairs of journals (network reciprocity: 0.04) (16). This was explained to a large extent by journal impact factor: Resubmission flows were oriented downstream overall, as far as impact factor is concerned (Fig. 2B). If a journal's manuscript rejection rate increased with impact factor, a similar pattern could be created even in the absence of active preference by authors. Therefore, we built random graphs expected if resubmission behavior were independent of impact factor (16). The change in impact factor would have a very different distribution under this null scenario (Fig. 2B, dashed line), even considering the observed higher propensity of high-impact journals to be the source of resubmissions (Fig. 2A). The skew in the distribution cannot be accounted for without invoking an active tendency of authors to move from high impact factor to low impact factors (Fig. 2B, solid line). Despite that, extremely negative differences (left tail of the distribution) were less frequent than expected, which indicates that authors adopt a risk-limiting strategy and preferentially make small leaps in impact factor in the course of resubmissions.

The second quantity that could contribute to journal centrality is the percentage of published articles that are first-intents (i.e., that were initially targeted at the publishing journal). Overall, 75% of all published articles were first-intents,

with a range of 67 to 87% across subject categories (table S1). None of the journals we sampled was found to be purely recycling manuscripts rejected from other journals. Thus, most articles were initially targeted to the journal that would eventually publish them (this conclusion is robust to any reasonable nonresponse bias) (16). This indicates that authors were overall efficient at targeting their research and limiting the risk of rejection.

Our results so far (Fig. 2) suggest that high-impact journals would attract many initial submissions and could select among them. In contrast, journals with low impact factors would more often receive and publish manuscripts previously rejected by higher-impact journals. This would create a positive association between impact factor and the proportion of published articles that are first-intents. Unexpectedly, we found an opposite pattern (Fig. 3): The proportion of first-intents decreased across the range of impact factors (Spearman rank correlation $\rho = -0.21$; $P < 0.001$) for all except the three topmost journals in our sample (Fig. 3). Although there is a lot of scatter, qualitatively similar trends were observed within most subject categories taken individually (table S4). One explanation is that high-impact journals, albeit preferred by authors, also experience stronger competition for manuscripts: They have a denser competitive neighborhood (as revealed by their more central position in the submission network) (Fig. 1 and fig. S4) and, together with high rejection rates, this makes them more likely to receive (and publish) resubmissions. As an example, even *Nature* and *Science*, which are certainly preferred journals in many cases, are far from publishing 100% of first-intents (Fig. 3),

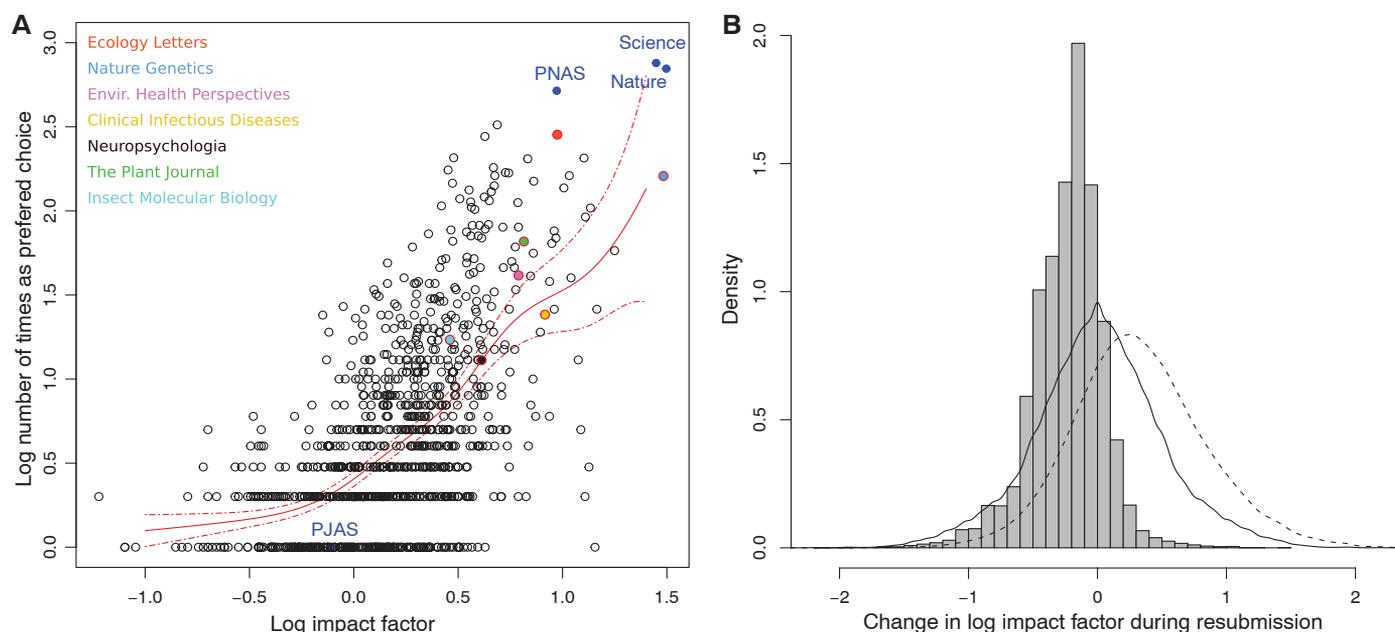


Fig. 2. Journal impact structures resubmission patterns. **(A)** The number of times a journal was first chosen for submission increases with impact factor. The average trend is shown as a red curve (± 2 SEM) (16). Multidisciplinary journals are highlighted in blue. One top journal per community is also highlighted (same color code as in Fig. 1). **(B)** The difference in impact factor

between the publishing journal and the one previously attempted is strongly skewed to negative values ($N = 18,078$). Mean difference in log impact factor: -0.23 , representing a 42% reduction on the natural scale. This differs from random graphs where the previously attempted journal was selected uniformly (dashed line) or in proportion to the values in (A) (solid line).

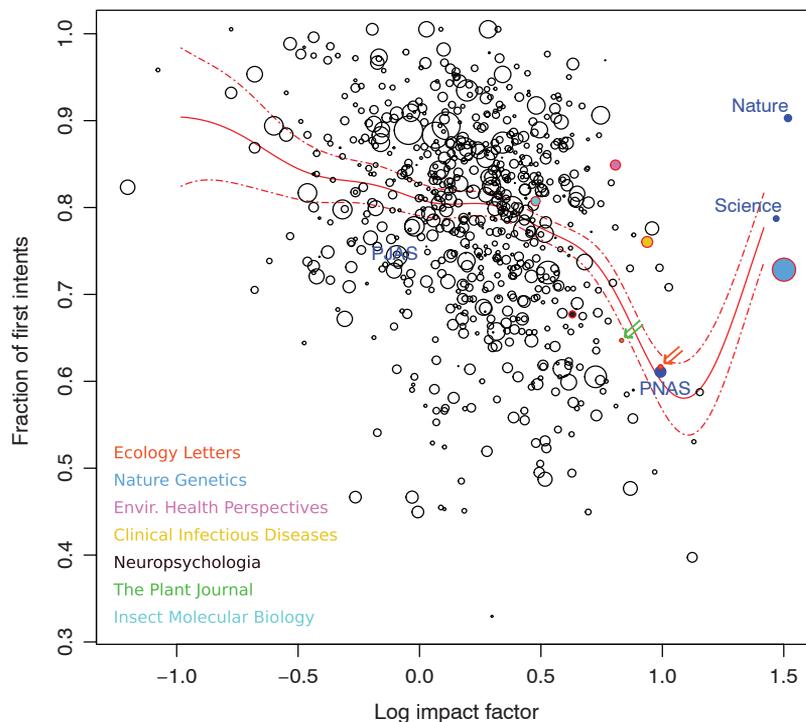


Fig. 3. High-impact journals publish proportionally fewer first-intent articles. Each circle is a journal (with area proportional to number of articles). The average trend is shown as a red curve (± 2 SEM) (16). For clarity, only journals with more than 20 articles are shown. Multidisciplinary journals are highlighted in blue. One top journal per community is also highlighted (same color code as in Fig. 1).

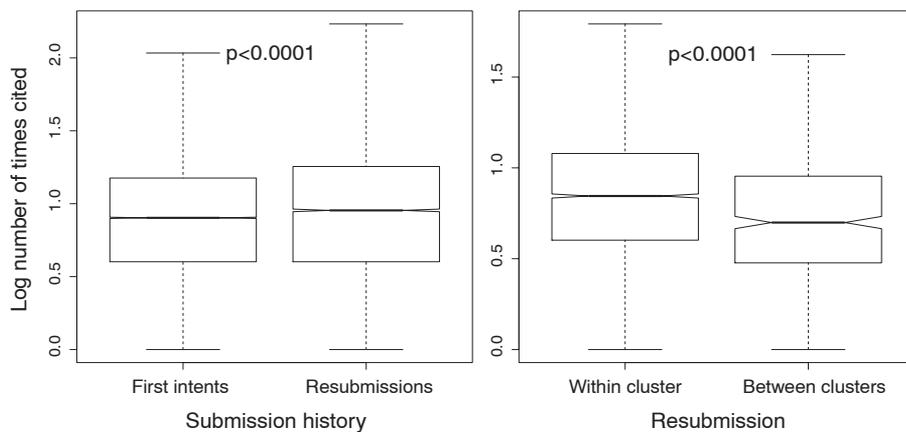


Fig. 4. Submission history affects citation counts. (Left) First-intent articles were less cited than resubmissions. (Right) Resubmissions were less cited if resubmitted between rather than within journal communities. Log-transformed citation counts are shown as box-whiskers plots (median/quartiles/range). P values are from permutation tests controlling for year and journal (16).

because each often publishes manuscripts rejected by the other. On the contrary, low-impact journals are more specialized, with a sparser competitive neighborhood and lower rejection rates in it. They receive proportionally fewer resubmissions from their neighbors.

Impact factor was here shown to affect the submission process, but does the submission process in turn affect citation counts and, thus, impact factor? Does submission history reflect the intrinsic “quality” or, in a more quantifiable way, the impact or utility of articles after publication?

We compared the number of times articles were cited (as of July 2011, i.e., 3 to 6 years after publication, from ISI Web of Science) depending on their being first-intents or resubmissions. We used methods robust to the skewed distribution of citation counts to ensure that a few highly cited articles were not driving the results (16). We controlled for year of publication, publishing journal (and thus impact factor), and their interaction (16). Resubmissions were significantly more cited than first-intents published the same year in the same journal (Fig. 4A).

This is challenging to explain because the submission history of articles is not public. With most resubmissions occurring from journals with higher impact (Fig. 2A), it could be that authors are able to assess the intrinsic quality of their research and its potential impact, so that manuscripts first submitted to high-impact journals, even when rejected, retained a higher propensity to be cited. However, this is unlikely because we found that resubmissions were more cited irrespective of their going up or down in impact factor (fig. S5). Several mechanisms could be involved, but perhaps the most likely explanation is that inputs from editors, reviewers, and the greater amount of time spent working on resubmissions significantly improve the citation impact of the final product. There are indications of the value of peer review from publication and editorial practice (15, 21). Our results suggest that it extends to citation impact. This validates the strategy of publishing groups that facilitate resubmission of declined manuscripts to other journals of the group (e.g., the Wiley Manuscript Transfer Program). Perhaps more important, these results should help authors endure the frustration associated with long resubmission processes and encourage them to take the challenge (14, 15).

An independent effect of manuscript submission history was that resubmissions occurring between two journals from the same journal community were significantly more cited than those between two different communities (Fig. 4B). This shows that, all else being equal, changing discipline during resubmission was a risky move, yielding lower-than-average impact after publication. Hence, the boundaries self-defined by author submission behavior (the journal clusters in Fig. 1) are reasonable in that transgressing them comes at a cost in terms of impact.

The network we have built from submission links (16) revealed that despite the prevalent fear of manuscript rejection (14, 22, 23), most published articles were initially targeted at the journal that would publish them and resubmission eventually paid off in terms of citation impact. Further aspects of the submission process could be investigated with this network, and it will be insightful to formally compare it to other social networks (9). Adapting existing analytical methods for submission flow data could form the basis of journal impact metrics closer to author perceptions (25, 26). Surveying a broader range of disciplines to compare their standards (9) would be feasible but quite time-consuming. Just as for citation analysis, a great step forward could come from concerted efforts at recording the meta-knowledge contained in manuscript flows.

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Research Council of Canada discovery grant to C.d.M. This research was approved by the Research Ethics Board of McGill. V.C. conceived the project, performed the survey, and processed the data. V.C. analyzed the data with inputs from E.D., K.G., D.R., and C.d.M. and wrote the manuscript with all authors.

Supplementary Materials

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Materials and Methods

Figs. S1 to S5

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Databases S1 and S2

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SAICAR Stimulates Pyruvate Kinase Isoform M2 and Promotes Cancer Cell Survival in Glucose-Limited Conditions

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Pyruvate kinase isoform M2 (PKM2) plays an important role in the growth and metabolic reprogramming of cancer cells in stress conditions. Here, we report that SAICAR (succinylaminoimidazolecarboxamide ribose-5'-phosphate, an intermediate of the de novo purine nucleotide synthesis pathway) specifically stimulates PKM2. Upon glucose starvation, cellular SAICAR concentration increased in an oscillatory manner and stimulated PKM2 activity in cancer cells. Changes in SAICAR amounts in cancer cells altered cellular energy level, glucose uptake, and lactate production. The SAICAR-PKM2 interaction also promoted cancer cell survival in glucose-limited conditions. SAICAR accumulation was not observed in normal adult epithelial cells or lung fibroblasts, regardless of glucose conditions. This allosteric regulation may explain how cancer cells coordinate different metabolic pathways to optimize their growth in the nutrient-limited conditions commonly observed in the tumor microenvironment.

An emerging hallmark of cancer cells is metabolic reprogramming, which includes elevated glucose uptake and oxygen-independent lactate fermentation called the Warburg effect (1–3). This reprogramming is necessary for the growth and survival of tumors (4) in stress conditions and in xenografts. However, the molecular basis for this event and its role in cancer growth have remained unclear.

Several proteins, including pyruvate kinase isoform M2 (PKM2), play important roles in the metabolic reprogramming and growth of cancer cells (4–6). PKM2 is one of four pyruvate kinases (PKs) found in mammals (7). It is highly expressed in fetal cells and cancer cells, whereas the other isoforms (PKM1, PKR, and PKL) are expressed in normal somatic tissues. Replacement of PKM2 in cancer cells with any other PK isoform drastically reduces cancer cell survival in stress conditions [hypoxia (4) or glucose depletion (8)] and suppresses tumorigenicity (4). This suggests that subtle differences between this tumor-

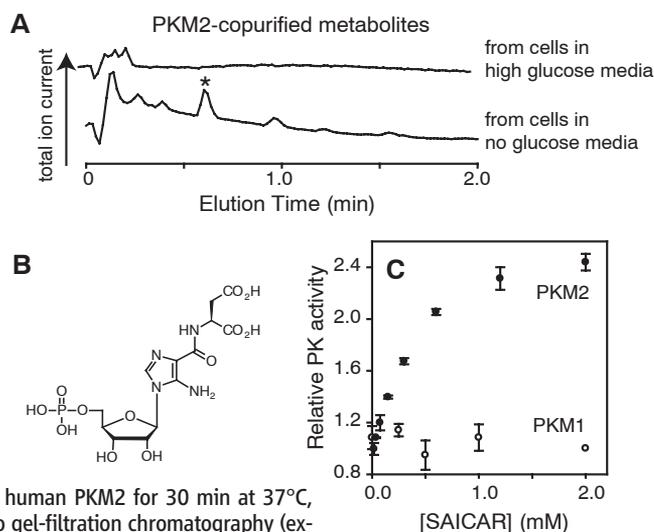
specific isoform and its normal cell counterparts are essential for tumor growth (4).

Biochemically, PKM2 is less active than its splice variant PKM1 owing to its higher Michaelis-

Fig. 1. Identification of SAICAR as a regulator of PKM2.

(A) LC-MS total ion current chromatographs of PKM2-copurified metabolites from glucose-rich (top) and glucose-free cells (bottom). A metabolite further characterized (fig. S1) is noted with an asterisk (*). A549 cells were incubated in fresh Dulbecco's modified Eagle's medium (10% dialyzed fetal bovine serum) containing either 25 mM or no glucose for 30 min, and used for metabolite extraction as described in materials and methods. Extracted metabolites

were mixed with recombinant human PKM2 for 30 min at 37°C, cooled on ice, and subjected to gel-filtration chromatography (exclusion limit: 10 kD) at 4°C. Metabolites that copurified with PKM2 were subjected to LC-MS analysis (C_{18} , electrospray ionization, positive mode). (B) Structure of SAICAR. (C) Effect of enzymatically synthesized SAICAR (fig. S2) on PK activities of (●) PKM2 and (○) PKM1. Data are means \pm SD ($n = 3$ independent experiments).



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