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FELLOWS NEWSLETTER

The Fellows Newsletter is published monthly by the Office of Education, Division of Intramural Research, National Heart, Lung, and Blood Institute and distributed to NHLBI DIR members to promote the interest of DIR Fellows.

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From the Director of the Office of Education

This month's column is inspired by a recent column by David Brooks in the New York Times. In this column, Brooks refers to the history of the founder of Pay-Pal, now a very successful businessman. During his education, he was very successful at competition, getting into Stanford University and then Stanford law school, and then a very prestigious clerkship with a U. S. Appeals Court. He was clearly on his way to success in law, and so competed for the prime training spot – a clerkship with the U.S. Supreme Court. However, he did not survive this competition, and went on to a career in business. He now lectures at Stanford, and one of the major themes echoed in his lectures is that winning in a competitive environment is not nearly as certain as making your own monopoly environment.

Once again, summer students are arriving on campus. I urge you all to take part in mentoring these students, as the experience you get is readily transferable to your next position.

Is Competition Healthy for Me?

By Herbert Geller, Ph.D.

Have you ever been scooped on a project? If you have, you know the frustration of seeing your results appear in print, but with someone else getting the credit. Even if you haven't been scooped, have you ever felt the pressure of competing with another lab? While competition is sometimes healthy, the steep differential between winning and losing creates a high level of anxiety and instability for all involved. So how can you avoid this situation?

In capitalist economics, competition is considered good, because it supposedly brings the costs down for the consumer, while monopoly capitalism is considered bad, because it creates a high cost situation and stifles innovation. However, what might be good for the consumer (competition) is not necessarily the best strategy for the seller: companies that establish and maintain monopolies based on innovative ideas or having unique approaches (think Google and Apple) flourish, while companies that start out in the lead and then fail to innovate sink (Sony or Kodak). It then follows that having a monopoly in a research area should lead to the most success, at least initially.

So how does one get to a monopoly position? In science, you achieve a monopoly by doing something truly unique or innovative. Under these circumstances, you do not need to worry about competition. I once had a colleague who did not read the literature – not at all. And when he was asked why, his response was that "*his work was the literature*". Of course, this did not come about

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THE SCIENCE BEAT

By Daniel Kraushaar, Ph.D.

Lee, I. H., Kawai, Y., Fergusson, M. M., Rovira, I. I., Bishop, A. J. R., Motoyama, N., Cao, L., & Finkel, T. (2012). Atg7 Modulates p53 Activity to Regulate Cell Cycle and Survival During Metabolic Stress. *Science336*, 225-228.

Cells respond to nutrient starvation by exiting from the cell division cycle. With prolonged nutrient deprivation, autophagy, the lysosomal degradation of cellular organelles, is initiated, and cell death pathways are simultaneously activated. Whether and how cell cycle control and cell death in response to metabolic stressare linked has so far remained unclear. The current NHLBI study by Lee *et al.* published in the journal Science, addresses the function of the essential autophagy gene, Atg7. Atg7 encodes an E1-like enzyme but its exact function in autophagy and cell cycle are only poorly defined. Using Atg7-deficient mouse embryonic fibroblasts (Atg7-/- MEFs), Lee and co-workers find that only about 20% of cells successfully exit from the cell cycle whereas around 60% of wild type cells abort S-phase entry three hours after acute nutrient withdrawal. This result highlights the role of Atg7 as a potential common nominator linking both cell cycle progression as well as autophagy and cell death upon withdrawal of nutrients. A series of follow-up experiments and biochemical assays further elucidated the underlying mechanisms of Atg7 function in both cell cycle and cell survival. Cell cycle arrest is commonly mediated by cyclin-dependent kinase inhibitors (CKIs) of the cip/kip family that include p21 and p27. As such, the expression of both p21 and p27 was compared between wild type and Atg7-/- MEFs. Serum starvation rapidly lead to accumulation of p21 protein as well as mRNA in WT cells and this response was largely absent in Atg7-deficient cells. In parallel, p21 promoter activity was lower in Atg7-/- cells and ChIP assays showed that endogenous Atg7 binds to the p21 promoter suggesting that Atg7 acts as a transcriptional activator of p21.Since p21 was also bound by the tumor suppressor p53, the authors asked whether Atg7 and p53 act in combination to transactivate p21 expression. Indeed, using epitope-tagged versions of Atg7 and p53 combined with immunoprecipitation, a physical interaction was demonstrated between the two proteins, which increased upon nutrient starvation. In vitro assays with truncated and point-mutated forms of Atg7 showed that both interaction with p53 and activation of p21 expression do not depend on the E1-enzymatic activity of Atg7, suggesting that enzymatic activity and regulation of expression by Atg7 are separable.

Analysis of additional genes regulated by p53 revealed that a subset of pro-apoptotic genes that include Noxa, Bax and Puma were expressed at higher levels in starved Atg7-/- MEFs. Furthermore cells deficient in Atg7 displayed higher levels of radical oxygen species and elevated levels of phosphorylated p53, both indicators of an increased DNA damage response. In line with an increase in the expression of pro-apoptotic genes and activation of a DNA damage response, Atg7-/- MEFs exhibited reduced survival upon starvation. Together these results suggest that Atg7 promotes cell cycle arrest via activation of p21 expression and promotes cell survival by suppressing activation of p53 and its associated activation of cell death and DNA damage response pathways.

Next, Lee *et al.* show that Chk2 is the upstream kinase required for p53 phosphorylation at Serine residue 20. Consistent with this idea, knockdown of Chk2 in the Atg7-/- background successfully rescued Atg7 deficiency. Both p53 phosphorylation and expression of Noxa, Bax and Puma were restored to approximatelywild type levels. The pro-survival effect of Atg7 was further illustrated in experiments with Atg7-/- knockout (KO) mice, which die shortly after birth. As in fibroblasts, metabolically active tissues of Atg7-/- mice displayed augmented expression of p53-dependent pro-apoptotic genes. Double KO of Atg7 and Chk2 rescued the expression of pro-apoptotic genes and achieved extended survival of mouse pups. Altogether, Lee *et al.* find convincing evidence that Atg7 orchestrates both cell cycle progression and cell survival. As such, nutrient withdrawal triggers the interaction between Atg7 and p53, which results in accumulation of p21 and cell cycle arrest. At the same time, Atg7 negatively regulates p53 activity through Chk2, which in net effect promotes cell survival. This multifaceted role of Atg7 will likely facilitate cell survival under detrimental conditions of metabolic stress when cells need to stop dividing while avoiding cell death.

Recognition to our Postbac Fellows

Post Bac Poster Day occurred on April 25th. Post Bacs from all institutes at the NIH participated in the event and were judged on poster and presentation skills. We'd like to recognize Sandy Hernandez (CBPC) and Kevin Rogacki (GDBC) who scored in the top 20%. Congratulations!

Sandy Hernandez (CBPC)

Kevin Rogacki (GDBC)

spontaneously, but arose because he picked a scientific area that was of significant importance, but approached it from an entirely new direction. Once he established his techniques, it became difficult for anyone to catch up quickly, and 15 years later, his lab is still defining the field.

Of course, novelty and monopoly are not synonymous with importance. I review many manuscripts that contain the phrase "*this is the first time that...*". My response is often "*it's because the problem is just not that important*". In addition, we have all heard stories about people whose research had difficulty because they were too far ahead of their time. (So here is where it helps to be a good salesperson). Conversely, some "hot" fields have more opportunities for success in publication because there is lots of interest (though there are few that have maintained their currency for the duration of a research career).

But remember, good science can be accomplished in an unpopulated or a crowded field – the choice is up to you.

- Meet new fellows
- Experience for your CV

Join the Fellows Advisory Committee! We are looking for new members.

Contact the Office of Education for more details

Poster Session Photos- 2012 NHLBI DIR Scientific Retreat

Recent Publications by NHLBI Fellows

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