Podcast Interview: Andrew Murray

PNAS: Welcome to Science Sessions. I’m your host, Rachel Wimmer. Himalayan Sherpas have evolved physiological features that allow them to survive low-pressure, low-oxygen conditions at high altitudes. Previous studies have suggested that enhanced mechanisms for the delivery of oxygen to tissues might enable Sherpas to survive at high altitude. However, whether metabolic adaptations that alter oxygen use by tissues underlie this ability was not clear. In a recent PNAS article, Andrew Murray and colleagues at the University of Cambridge evaluated a group of lowlanders and Sherpas on a research expedition during which the study participants ascended to a height of 5,300 meters, from Kathmandu to Mount Everest Base Camp. I recently spoke with Murray on the phone to discuss his work on the metabolic adaptations of Sherpas. Murray begins by explaining how the human body typically responds to low-pressure, low-oxygen conditions.

Murray: So when somebody goes to high altitude, quite typically the first things you see is proximate increase in their resting heart rate or an increase in their heart rate. But given enough time, you start to see some longer term changes. So perhaps an increase in red blood cell counts – that might kick in after a week to two weeks. And then maybe with a bit more long term acclimatization, you might see an increase in the number of capillaries delivering blood to the tissues. But of course that’s all in lowlanders and these are people who are not adapted to altitude. You see a different set of responses, or a different set of features really, in the some of the populations that live at high altitude and that have lived there for many thousands of years.

PNAS: What are some of the physical characteristics of Sherpas that allow them to perform well at high altitudes?

Murray: We were focused in particular on how the Sherpas’ muscles uses oxygen. And the reason we hit upon that, we thought there must be a metabolic difference in the Sherpas for a number of reasons. The first clue was that if you look at Sherpa red blood cell counts at altitude and you compare them with lowlanders, at any given altitude, they actually have fewer red blood cells. So it suggests that they have lower oxygen concentrations in their blood. So it seems it’s not simply how much oxygen you’ve got, but what you do with it that counts. The advantage to having lower red blood cells means that the blood is less thick, its less viscous, and it might flow more easily so there could be an advantage there allowing them to actually take more oxygen to the muscles despite the fact that they’ve got fewer of the oxygen carrying cells. But on top of that, some genetic evidence suggested that various metabolic pathways were also altered in this group. The one gene that was flagged up by a group working in California was a
gene called PPARα, or PPARα is the protein that it encodes. And when it’s activated, it turns on fat oxidation. So fat is a great fuel. It’s great because it’s very energy dense. You get a lot of calories out of a gram of fat, more than you do out of a carbohydrate. But the tradeoff is that it’s very oxygen hungry — in order to get the ATP out, the cells energy currency, you need to invest a lot of oxygen to get it out of fat. So under normal sea level conditions, it makes sense to burn fat. But when you go to altitude and oxygen becomes limiting, it makes sense to switch to a more efficient fuel like glucose. So our hypothesis was that this genetic variant would decrease fat oxidation in the high altitude groups in particular in the Tibetan group, which we’ve seen, and possibly in the Sherpas.

**PNAS:** How did you measure differences in fat oxidation in Sherpas and lowlanders at altitude?

**Murray:** So we set about measuring this in a group of Sherpas and a group of lowlanders, first of all at low altitude and we took muscle biopsies from the top of their thigh. We did some live measurements of fat oxidation capacity in those muscle biopsies and froze samples and brought them back to the lab for other analysis. And then both groups followed a standardized ascent to Everest base camp at 5,300 meters. So our lowlanders were huffing and puffing their way to get there, the Sherpas it’s like a walk in the park. And we take another muscle biopsy at Everest base camp and repeated those live measurements there at base camp of oxygen consumption in the muscle. And essentially what we found was that even at baseline, the Sherpas were using their oxygen more efficiently. In other words, a greater proportion of it was going towards making ATP without being wasted. The big surprise for us was that in the Sherpas, the ATP levels actually increased in their muscle and phosphocreatine increased when we took them at altitude despite the lack of oxygen. So it looked like a healthier profile. We also measured markers of stress, oxidative stress, which can occur at altitude which might help to start making free radicals and it increased in the lowlanders. Again in the Sherpas, there was no response to the low oxygen. They didn’t produce these markers of stress.

**PNAS:** Do these findings have clinical implications?

**Murray:** I’m really interested in low oxygen levels in disease situations. And you find this in a number of diseases, so lung failure, heart failure, anemia, many cancers find low oxygen levels, condition known as hypoxia. Most importantly for some of my colleagues who work in intensive care units, you see a lot of very, very sick patients. Any disease in its most severe form can find you in intensive care. They see huge mortality in these patients, up to about 20%. Even those that recover don’t always regain full function after they do recover. And the interesting thing with these patients is that almost all of them have either low oxygen levels in their blood or an apparent inability to use that oxygen. Now one of the first things that would typically happen to these
patients is that the clinician would try to do something to try to elevate their oxygen levels. But there's very little evidence that it actually does them any good, in fact some evidence, and a growing body of evidence, that it's doing them some harm. So the question really is not how do we restore their oxygen levels, but how to we help them to tolerate low oxygen levels in the clinic. The challenge now is to try to work it out to translate these findings, can we come up with a therapeutic strategy that makes a patient a little bit more Sherpa like and allows them to survive that hypoxic condition in the clinic. Perhaps we can learn a lesson from the Sherpas. They seem to be the masters of tolerating low oxygen levels, surviving in low oxygen levels at altitude and even thriving.

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