

WEBVTT

NOTE duration:"00:19:44.728000"

NOTE language:en-us

NOTE Confidence: 0.934953570365906

00:00:00.020 --> 00:00:06.770 We've been doing in my lab trying to understand this link between obesity and cancer and how we might be able to intervene.

NOTE Confidence: 0.914195656776428

00:00:07.410 --> 00:00:37.480 So we're doing this work because as likely everyone in this room is aware there's a strong link between obesity and several tumor types. the CDC has now associated 13 tumor types with an increased risk and a poorer prognosis occurring with obesity and it seems that there may be others on the horizon and with rising obesity rates in the US and really worldwide. This is meant that obesity has now become the second leading cause of preventable cancer deaths in the United States second only to smoking.

NOTE Confidence: 0.944330096244812

00:00:37.480 --> 00:00:43.080 So that means that we really need to understand what causes this link between obesity and cancer so that we can intervene.

NOTE Confidence: 0.907697796821594

00:00:44.930 --> 00:00:59.770 So there have been a number of potential tumor promoting factors that have been associated with obesity. And here are just a few inflammatory cytokines glucose insulin fatty acids. IGF one at a connect and leptin and sex hormones and many others.

NOTE Confidence: 0.909889876842499

00:01:00.290 --> 00:01:14.600 And and realistically it's probably all of these factors converging but the work that my lab has been doing focuses on understanding the link between obesity insulin and cancer and how that might be mechanistically promoting tumor growth.

NOTE Confidence: 0.896669149398804

00:01:15.330 --> 00:01:47.770 It turns out that tumor insulin signaling is dynamically regulated in this study, we performed an oral glucose tolerance test, giving mice a dose of glucose that mimics what happens under postprandial conditions. So if you ate a very high carbohydrate meal and then we looked at a readout of insulin signaling asked phosphorylation in implanted subcutaneous colon adenocarcinoma tumors and we find that the time course of plasma insulin concentrations, they as you might predict they go up quite quickly and then fall off.

NOTE Confidence: 0.898443996906281

00:01:47.770 --> 00:02:09.610 Normalizing by 2 hours and asked phosphorylation in the tumor follows that pretty closely indicating that over the course of the day there might be dynamic changes in tumor insulin signaling that could contribute to tumor growth in Katy is certainly a growth factor and so this could be 1 read out of insulin being linked to tumor growth.

NOTE Confidence: 0.904823422431946

00:02:10.420 --> 00:02:25.210 So based on that we performed this study, the inaugural paper for my lab published last year to test the hypothesis that hyperinsulinemia, resulting from insulin. Resistance would drive colon tumor growth in obese high fat fed mice.

NOTE Confidence: 0.909165859222412

00:02:26.730 --> 00:02:57.740 In this study to test that hypothesis. We first treated animals with metformin. The most commonly prescribed anti diabetes drug worldwide and not surprisingly, we found that it lowered fasting plasma glucose and insulin concentrations to test the relevance of this reversal of hyperinsulinemia. We also took a group treated with metformin and gave them back replacement insulin by subcutaneous insulin pellet. This would allow us to dissociate plasma glucose concentrations, which of course were lowered when we gave insulin from plasma insulin?

NOTE Confidence: 0.876930475234985

00:02:57.740 --> 00:03:02.080 Which is normalized with the insulin subcutaneous insulin infusion?

NOTE Confidence: 0.885426878929138

00:03:02.800 --> 00:03:33.570 And what we see is that while high fat feeding has a profound impact to accelerate tumor growth metformin treatment reverses that through an insulin dependent pathway. So when we treat with metformin tumor growth rate slow to about 1/4 of what they were simply on a high fat diet and growth rates are way back up when we restore hyperinsulinemia, suggesting that this is an insulin dependent effect of metformin to slow tumor growth. Unfortunately metformin is a bit of a messy agent.

NOTE Confidence: 0.895132958889008

00:03:33.570 --> 00:04:04.620 To use to test this hypothesis because it does accumulate in tumors as you likely are aware. There have been a number of studies over recent years, giving metformin primarily in vitro and actually showing a direct effect of metformin to slow tumor cell division. But the important point about that is that to get that effect to slow cell division. You have to give very, very high millimolar concentrations of metformin concentrations that would never be measured in plasma or likely tumor of patients who are treated and so to test the relevance of.

NOTE Confidence: 0.89902651309967

00:04:04.620 --> 00:04:26.730 Pharmacologically relevant doses of metformin we measured metformin concentrations in plasma and tumor by mass back and find them to be quite low around 100 micromolar and when we put those pharmacologically relevant doses of Metformin. An MC 38 cells in vitro. We have absolutely no effect on cell division again, suggesting likely not a direct effect in this context.

NOTE Confidence: 0.892834544181824

00:04:27.750 --> 00:04:58.340 So our alternative hypothesis that we pause. It is that instead of acting directly on the tumor that metformin is likely slowing tumor growth in high fat. Fed mice by an effect on glucose metabolism by reducing insulin responsive tumor glucose uptake and oxidation to test that hypothesis of course, we measured these parameters and we find that glucose uptake is indeed hormone responsive. It's reduced by 50% by reversing hyperinsulinemia with metformin treatment and restored when we give back insulin.

NOTE Confidence: 0.904629349708557

00:04:58.940 --> 00:05:29.510 And that's all well and good, but Unfortunately just measuring glucose uptake only tells half the story. It doesn't tell us what the cell does with glucose once it takes it up and so to figure that out, we developed a stable Isotope, Mass. Spec method to be able to measure the ratio of tumor glucose oxidation to total mitochondrial oxidation and we find that again metformin treatment reduces that parameter by 50% and insulin restores. It importantly this is evidence against the Warburg effect being the only important.

NOTE Confidence: 0.851308047771454

00:05:29.510 --> 00:05:41.130 Parameter of glucose metabolism, contributing to tumor growth because we show here that not only glucose uptake, but also oxidation is dynamically regulated by insulin.

NOTE Confidence: 0.887840569019318

00:05:43.430 --> 00:06:15.460 So we believe that these data show that metformin is slowing tumor growth by an indirect effect to improve to lower plasma insulin levels. But because it is a messy agent and as I said does accumulate somewhat in tumors. We wanted to use an alternative insulin lowering agent that might be a bit cleaner and Fortunately we developed such an agent. A couple years ago and insulin sensitizer hepatic insulin sensitizer, which we call controlled release. Mitochondrial protons 4 or CRMP. This is simply a controlled release version of the classic mitochondrial.

NOTE Confidence: 0.803761422634125

00:06:15.460 --> 00:06:19.580 Cortana, 4, two fourth dinitrophenol with a controlled release coding.

NOTE Confidence: 0.890150845050812

00:06:20.180 --> 00:06:53.710 Because it's an unpopular it increases hepatic mitochondrial oxidation increasing it. About 2 fold in high fat fat animals and it does so safely because of the altered pharmacokinetics when we compare the peak plasma concentrations of the toxic dose of unaltered DNP to the effective dose of CR MP. We find that peak plasma concentrations are about 100 fold lower whereas the half life of the drug is much longer. We find that the toxicity of uncouplers relates to their peak plasma concentrations in the efficacy relates to the.

NOTE Confidence: 0.910066306591034

00:06:53.710 --> 00:07:07.340 Area under the curve and so this would predict that this drug would be much safer and more effective and in fact that is what we see a 500 fold improvement of the toxic to effective dose ratio simply by putting that controlled release coding and EMP.

NOTE Confidence: 0.893806576728821

00:07:07.990 --> 00:07:15.410 And it works when we give it to animals mixed up in a little bit of peanut butter. It increases hepatic mitochondrial fat oxidation.

NOTE Confidence: 0.898275434970856

00:07:16.170 --> 00:07:35.480 Reverse is non alcoholic fatty liver disease by burning liver fat improving hepatic insulin sensitivity, lowering gluco. Neo Genesis and reducing fasting fat, fasting and postprandial plasma insulin concentrations and of course, it's this reversal of hyperinsulinemia. That's most important for testing the insulin hypothesis here.

NOTE Confidence: 0.891495883464813

00:07:36.660 --> 00:08:07.830 So we hypothesized of course, that controlled release. Mitochondrial Cortana for would also slow tumor. Growth in high fat. Fed mice in an insulin dependent manner by reducing tumor glucose uptake and oxidation when we treat MC 38 tumor bearing mice with this controlled release. Mitochondrial Cortana for we find that it does indeed reverse non alcoholic. Fatty liver disease and also normalizes skeletal muscle triglyceride content. Now that might be a little bit of a surprise because I told you that this agent is functionally liver targeted it.

NOTE Confidence: 0.885333299636841

00:08:07.830 --> 00:08:38.550 Only increases fat oxidation in the liver and it turns out that this reversal of the diet induced increase in skeletal muscle triglycerides is also due to that reversal of Nafld. When you reverse non alcoholic. Fatty liver disease. You have a reduction in hepatic. VLDL export and that reduction in liver triglyceride export leads to this normalization of skeletal muscle content. So the Uncoupler CR MP is doing all the right things, normalizing liver and skeletal muscle fat? What does it do to plasma glucose and insulin?

NOTE Confidence: 0.912534773349762

00:08:39.030 --> 00:08:46.610 Doing all the right things their CR MP reverses the high fat diet induced increases and fasting plasma glucose and insulin concentrations.

NOTE Confidence: 0.853568136692047

00:08:47.450 --> 00:09:14.350 And again to test the physiologic impacted this reversal of hyperinsulinemia. We also took a group of CR MP treated mice and gave them back insulin by subcutaneous pellet when we measure tumor size. We find that high fat feeding only accelerates MC 38 tumor growth. But this is reversed by CR MP treatment in an insulin dependent manner. When we restore hyperinsulinemia. We reverse the effect of CR MP to slow tumor growth.

NOTE Confidence: 0.871308326721191

00:09:15.400 --> 00:09:32.600 It also has the hormone dependant effects that you might expect and tumor glucose metabolism. We find in this model also glucose uptake and oxidation are hormone driven increased with obesity normalized with CR MP and restored by replacement hyperinsulinemia.

NOTE Confidence: 0.856760919094086

00:09:34.190 --> 00:09:56.940 So CRP works and metformin works in MC 38 tumor bearing mice. What about a second model of colon adenocarcinoma here. We studied APC. Min heterozygous mice. This is a mouse model of familial adenomatous polyp. Oasys, a condition that is also exacerbated with diet induced obesity and we find in this model again. CR MP normalizes fasting plasma glucose and insulin.

NOTE Confidence: 0.869206249713898

00:09:58.030 --> 00:10:23.890 It normalizes the increases in Pollock glucose uptake an oxidation that we see with diet induced obesity and this is in an insulin dependent manner because restoring hyperinsulinemia. Abrogates these effects, so these data really speak to the hormone responsive AT of tumor glucose uptake and oxidation indicating that glucose uptake and oxidation aren't constituent if Lee High, but may actually be regulated by hormonal and or dietary factors.

NOTE Confidence: 0.868005931377411

00:10:25.180 --> 00:10:42.390 But what effect does it have on the polyps well the Histology really tell the story. The polyps we can see here in Brown with this beta catenin stain. You can tell they're much smaller in the Chow and CR MP treated animals than they are in high fat fed animals and those treated with replacement insulin.

NOTE Confidence: 0.852807521820068

00:10:43.020 --> 00:10:47.350 And survival was prolonged pretty substantially here.

NOTE Confidence: 0.903201937675476

00:10:48.580 --> 00:11:19.390 So we're very excited about these data. But Unfortunately our uncoupler. CR MP is not in the clinic. Yet it has just published a study in nonhuman primates. It's looking like it's likely to move that way or at least a derivative of this uncoupler, but it's not there yet. So we wanted to say what could we do with an insulin lowering agent that is already in the clinic. We've done it with metformin, but the concern about metformin is that it acts primarily as an inhibitor of gluconeogenesis. So it will lower fasting plasma glucose concentrations and have some effect on postprandial.

NOTE Confidence: 0.889278531074524

00:11:19.390 --> 00:11:50.230 But it's not a glucose waster what we really want to do is give a drug that has a profound effect on both fasting and postprandial insulin glucose and insulin concentrations and that could just be dhapakhel flows in or another. SG LT2 inhibitor. SG LT2 Inhibitors. Of course cause. It's pretty significant glyco Syria and so the individual gets rid of a whole lot of glucose through the urine and has a larger reduction in glucose and insulin area under the curve over the course of the day at least in mice, then we see with met Foreman and so when we give.

NOTE Confidence: 0.825891673564911

00:11:50.230 --> 00:12:11.840 This SG LT2 inhibitor to MC 38 tumor bearing mice, we find again that tumor glucose uptake and oxidation are normalized in high fat. Fed Mistah Chao said rates and this corresponds to a large impact on tumor size, whereas high fat feeding accelerates tumor growth. Dappa slows it to what we measure in the Chow said mice through an insulin dependent pathway.

NOTE Confidence: 0.910986304283142

00:12:13.210 --> 00:12:30.360 So we're very excited about these this impact of insulin lowering agents and colon cancer but are these findings going to translate to other obesity associated tumor types as I showed you there are 13 tumor types. So far that have been associated with obesity and so we want to know if we may have an impact in more than just colon cancer.

NOTE Confidence: 0.909397661685944

00:12:30.950 --> 00:13:02.780 And so very talented student I had working with me. Aviva did this in vitro study where she took several different tumor cell lines. Some associated with obesity on the left colon cancer breast cancer and prostate cancer and others, not associated with obesity. Melanoma B cell lymphoma and small cell lung cancer and she finds that when she incubates. These cells in physiologically relevant concentrations of insulin. There is an impact to increase the ratio of glucose oxidation to total mitochondrial oxidation.

NOTE Confidence: 0.89664214849472

00:13:02.780 --> 00:13:20.230 Only in those obesity associated tumor types, but no relationship in the obesity. Independent ones, and what's most important is this impact on cell division. We see a dose dependent effect of insulin to accelerate tumor cell division in the obesity associated tumor types, but not in the obesity independent.

NOTE Confidence: 0.911080837249756

00:13:22.170 --> 00:13:54.200 These findings may actually translate to humans, so an excellent MD. PhD student. I have working with me. Brooks Leitner did this analysis of publicly available pet scan images where he compared tumor types that are associated with obesity versus not and he finds that in both head and neck. Squamous cell carcinoma and soft tissue sarcoma, which are not associated with obesity. There's no relationship between body mass index and tumor glucose uptake, whereas in small cell lung cancer, which several reports have suggested.

NOTE Confidence: 0.905012011528015

00:13:54.200 --> 00:14:25.410 Obesity may actually be protective in that cancer, although that certainly still up for debate. There was a negative correlation between BMI and tumor glucose uptake, whereas in breast cancer, which has one of the strongest associations between obesity and tumor cell division. We see a positive correlation between BMI and tumor glucose uptake now. Obviously, what we'd really like to do is have plasma insulin concentrations on the X axis here and so, if there are any clinicians in the room interested in collaborating on that study. I'd love to talk to you afterward.

NOTE Confidence: 0.909635841846466

00:14:25.410 --> 00:14:33.370 But these data. We think are at least suggestive of a relationship between some parameter related to obesity and tumor glucose metabolism.

NOTE Confidence: 0.889622688293457

00:14:34.530 --> 00:15:04.840 So we did in the final part of the talk. I'll show you data where we hypothesize that both of our insulin, lowering agents would slow obesity associated tumor growth in a second cancer type breast cancer in an insulin dependent manner. So here we studied mice in a mouse model of triple negative breast cancer and we treated them with CR MP and find that again in this model of breast cancer tumor glucose uptake and oxidation are hormone responsive accelerated with diet induced obesity reversed.

NOTE Confidence: 0.845848441123962

00:15:04.840 --> 00:15:08.720 With the RMP treatment and restored by replacement hyperinsulinemia.

NOTE Confidence: 0.895056307315826

00:15:09.690 --> 00:15:22.480 And what impact does that have on tumor size well again in this mouse model of triple negative breast cancer high fat diet accelerates tumor cell division, but it's normalized by normalizing hyperinsulinemia with CRMP.

NOTE Confidence: 0.885710835456848

00:15:23.250 --> 00:15:28.490 And brought back up when we get back insulin to restore hyperinsulinemia in this model.

NOTE Confidence: 0.84873765707016

00:15:29.790 --> 00:15:42.870 And Secondly with Dappa again. We find an insulin dependent effect on tumor glucose uptake and the ratio of tumor glucose oxidation to total mitochondrial oxidation that is insulin mediated.

NOTE Confidence: 0.842638492584229

00:15:43.420 --> 00:15:52.890 Translating to an effective dappa to slow E 0771 tumor cell division that again is insulin dependent.

NOTE Confidence: 0.909042716026306

00:15:53.450 --> 00:16:24.340 And finally I'll end with exercise, which is an intervention that we know is insulin sensitizing there have been a number of trials done both at Yale and elsewhere to look at the impact of exercise in breast cancer as well as several other cancers and we know epidemiologically that exercise is protective reduces the incidence and improves the prognosis of those with breast cancer at just about any stage but we really don't fully understand what the mechanism for this is and to what extent it's driven by the insulin sensitizing effect of exercise.

NOTE Confidence: 0.883333623409271

00:16:24.340 --> 00:16:54.730 And so that's a question, we're addressing in future studies. So I took some mice and gave them access to voluntary running wheel so that they could run anytime. They wanted it's very impressive a mouse will run about 7 kilometers if you give it access to a running wheel, which is many thousands of kilometres of inhuman if we were to do that based on body size and this clearly isn't insulin insulin sensitizing intervention plasma insulin concentrations are reduced by more than 50% in the exercising mice.

NOTE Confidence: 0.890877604484558

00:16:54.730 --> 00:17:27.580 And this slows tumor growth rates if anything, the tumor growth is looking even a little bit lower than the child fed animals. Even in these high fat fat animals that are exercising and so the next series of studies will be in my sweetie. 0771 tumors that lack the insulin receptor and so we can see to what extent this effect of exercise to slow tumor growth may or may not be insolent dependent so with that. I hope I've convinced you in this talk that hyperinsulinemia is indeed driving tumor growth in mouse models of breast.

NOTE Confidence: 0.878669261932373

00:17:27.580 --> 00:17:28.650 And colon cancer.

NOTE Confidence: 0.907170832157135

00:17:29.160 --> 00:17:39.300 And that insulin lowering agents may be beneficial in slowing tumor growth at least in part by a reversal of insulin stimulated increases in tumor glucose uptake and oxidation.

NOTE Confidence: 0.902639508247375

00:17:39.800 --> 00:17:51.200 And with that I'll close I'd like to acknowledge the folks in my lab have done a lot of this work. Our collaborators as well as our funding sources and I'd be very pleased to take any questions, you may have.

NOTE Confidence: 0.675512790679932

00:17:53.550 --> 00:17:56.830 Question.

NOTE Confidence: 0.880877673625946

00:17:57.760 --> 00:18:28.120 So I'll start Rachel, the effects of the glucose and insulin lowering treatments seemed to bring it back down to baseline of the high non high fat diet. One could imagine that it could have actually gone beyond that, like the exercise any thoughts or explanations for that. It sort of reverses the high fat diet right. You know it's never going to get it down to 0. I mean insulin doesn't go down to 0, either when we give these interventions, it would be an?

NOTE Confidence: 0.890766263008118

00:18:28.120 --> 00:18:49.750 Actually, uh the next series of studies will be to combine potentially curative therapies with these insulin lowering agents. Both immunotherapy and chemotherapy to see if we can actually cure. These animals because that's certainly what we really want to do and it seemed like also your folks in really on the insulin affect specifically in these models exactly as well. Other folks with questions.

NOTE Confidence: 0.746072232723236

00:18:51.850 --> 00:18:54.160 Thank you.

NOTE Confidence: 0.532914936542511

00:18:54.890 --> 00:18:56.340 Does

NOTE Confidence: 0.901167333126068

00:18:57.170 --> 00:19:28.340 So, your data suggests that glucose oxidation might be the important metabolic driver in this system do you have you ruled out all other metabolic pathways? Now certainly not the glucose oxidation metabolism? Is associative data? I think realistically we probably have increased increased or decreased glycolysis at that also tracks with increased or

decreased oxidation. There are inhibitors and activators of pyruvate dehydrogenase and so giving those agents in combination with these metabolic therapies would really be the best way to test.

NOTE Confidence: 0.859322845935822

00:19:28.340 --> 00:19:39.400 The impact specifically of oxidation have you used other inhibitors of the DC cycle to see if you got a similar effect. Not yet but that's that's a great experiment and we're certainly planning to thank you. Thank you.