Kinase Movie Script
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The Heart of Research and Discovery in Dundee Audience: Scientists and Schools

During the course of our lives, many of us will be affected – either directly or indirectly ---- by diseases whose molecular bases share a common thread. Hypertension, neurodegeneration, or cancer for example -- how often do we stop to consider the events that occur during the course of diseases such as these?

Or the important role that communication plays in the process of their outcomes?

While we all recognize the importance of communication between people did you know how critical this process is *within* each of us? Or that the cells and tissues that make up our entire body convey key pieces of information to each other, not by talking to one another but via what's termed as 'signalling events'?

This is what scientists around the world are working hard to understand

And here in Scotland the MRC Protein Phosphorylation and Ubiquitylation Unit is at the forefront of this research for it turns out that one of the major means by which cells 'signal', and thereby communicate is through a mechanism termed phosphorylation.

Now, it has been known for awhile that phosphorylation is intimately intertwined with an enzyme class known as kinases….

But I'm getting ahead of myself…..let me start at the beginning

Phosphorylation is the addition of a phosphate group to something – a protein, or a fat molecule for example.

The fact that phosphates could be found covalently attached to proteins was discovered in 1906 in a protein found in egg yolk.

The discovery of the result thus came before the identification of the enzymes that attach and remove phosphate because it took a little longer for scientists to identify the proteins that were responsible for this process

In fact, it wasn't until 1954 that the first enzyme that catalyzes the addition of a phosphate to a protein was found using crushed liver cells and a protein abundantly found in milk. Casein kinase, or CK2, was the first kinase ever discovered.

At about the same time, the first protein phosphatase was identified. A phosphatase is an enzyme which removes phosphates from proteins

Thus another piece of the puzzle was solved.

Today we know that there are numerous enzymes that add or remove phosphate to or from other target proteins. Why then are we still talking about phosphorylation?

It all stems from findings that were occurring close to the time that protein kinases were identified....

Around the same time that scientists in the 1950's discovered casein kinase, other scientists had been working on another protein that had perplexed them for years. This protein, called glycogen phosphorylase, was known to exist in two forms – an active form (a) and an inactive form (b) -- but until the mid 1950's, no one knew precisely what made them different

Scientists did know that the b form could be converted to the a form when adrenaline was released

The key to unlocking the importance of kinases and phosphorylation occurred in 1955 when Drs. Fischer and Krebs realized that the interconversion of phosphorylase 'b' and 'a' involved the addition and removal of a phosphate group.

Thus Drs. Fischer and Krebs had ultimately figured out how signals in the body were converted into biochemical changes in cells – that could be reversed! For this, they both received the Nobel prize in Physiology.

This reversible phosphorylation of proteins is now known to regulate nearly every aspect of cell life and many biological processes – which is precisely why we're still talking about it today!

Phosphorylation and dephosphorylation, catalysed by protein kinases and protein phosphatases, can modify the function of a protein in almost every conceivable way, for example by:

- Increasing or decreasing its biological activity
- Stabilizing it or marking it for destruction
- Facilitating or inhibiting movement between subcellular compartments, or even
- By initiating or disrupting protein–protein interactions.

The simplicity, flexibility and reversibility of phosphorylation explains why it has been selected as the most general regulatory device adopted by eukaryotic cells.

Importantly, abnormal phosphorylation has been identified as the cause or consequence of many human diseases.

Thus scientists in academia and the pharmaceutical industry are working hard to identify ways to modify kinase activity as a means to alter the course of disease progression.

This would be easy if there were just one kinase or phosphatase.

But from that humble beginning with the first kinase identified, more enzymes were discovered until in 2002, a comprehensive catalogue of all human protein and lipid kinases and phosphatases was built whereby we now know of over 500 human kinases and 140 phosphatases.

The MRC Protein Phosphorylation & Ubiquitylation Unit based at The University of Dundee in Scotland, is perhaps the largest and most prolific center studying these enzymes worldwide. The Unit was established in 1990 based on the research efforts initiated and led by Sir Philip Cohen beginning in 1971 after he trained with Drs. Fischer and Krebs.

It now counts amongst its team, almost 200 scientists from around the world, whose primary focus is to better understand these signals in health and disease.

Given the expertise housed in Dundee around these proteins, it is not surprising that the pharmaceutical industry has not only taken notice but had a long-standing partnership with the Unit that began in 1998

This collaboration with industry has yielded tangible results – including an approved drug for treatment of a specific form of skin cancer

While a great start, we're by no means finished yet – as there will always be new challenges in science. And our research can help us and the world better understand, and hopefully cure, diseases. Our mission, is to move science forward.