Identifying Possible Therapeutic Targets in Kinase Fusions

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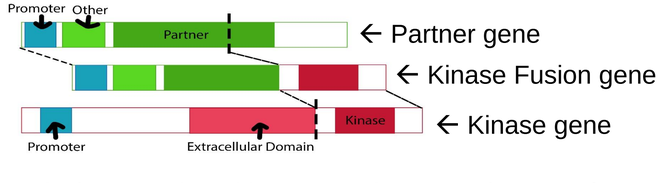
Abstract:

In recent years kinase fusions have begun to emerge as a rapidly growing field of research in cancer treatment. In this review I explored the frequency, structure, and mechanisms of kinase fusions. Similarities between fusions were explored for each of these aspects by comparing studies on individual kinase fusions. This revealed that dimerization domains were provided by most fusion partner genes and allowed constitutive activation of the kinase domain through ligand independent dimerization. These dimerization domains therefore provide the most promising area to explore for new treatments.

Introduction:

Kinase fusions are the products of **chromosomal rearrangements** that join the kinase gene with a fusion partner. The resulting protein often has **aberrant activation** of the **kinase domain** due to its fusion partner.



Importance:

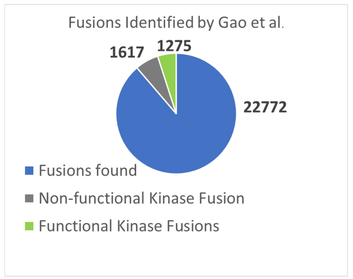
- Kinase fusions are found in **16.5%** of cancers (Gao et al. 2018).
- Found in wide variety of rare and common cancers.
- Treatment with **tyrosine kinase inhibitors** (TKIs) is effective but fusions displaying **resistance** have already been identified.

Aims:

- Understand kinase fusion **formation**, **structure** and mechanism of **activation**.
- Find **recurrent features** of fusions for possible treatments.

Frequency of Kinase Fusions

A study by Gao et al. investigating fusions in cancer found **2,892** kinase fusions in 9,624 tumours.



- **1,275** of the kinase fusions had **functional kinase domains** meaning they could be activated.

It is known that fusions are found in most cancers and that they display different prevalence depending on the cancer type. For instance, **thyroid carcinoma** (THCA) displayed the highest amount of fusions.

Activation of Kinase Fusions

It is crucial to understand the activation of kinase fusions to be able to combat their oncogenic potential.

Dimerization:

As with wild type kinase receptors, kinase fusions are also activated by **dimerization.** This activation becomes oncogenic as the fusion partners provide **dimerization domains** which allow **ligand independent dimerization** of the fusions and thus upregulated activation.

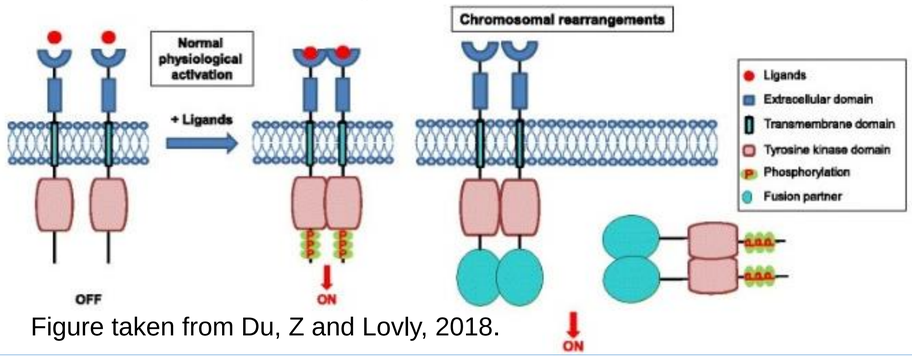


Figure taken from Du, Z and Lovly, 2018.

Transcriptional regulation:

Due to the chromosomal rearrangement some fusions are regulated by the partner genes' **promoters**. This leads to **increased expression** and effects fusion prevalence in different cancers. For example, the **SLC45A3-FGFR2** fusion is expressed by the **androgen-regulated** SLC45A3 promoter and leads to its oncogenic potential in **prostate cancer** (Tomlins et al., 2005).

Removal of Regulatory domains:

Kinase receptors often have other domains such as extracellular domains that are replaced by the fusion partner. These domains often contain **regulatory sequences** that which when **lost** allow **increased activation**. As seen in **TPR-MET** and the loss of **Ser98** residue that regulates **tyrosine phosphorylation.**

Structure of Kinase Fusions:

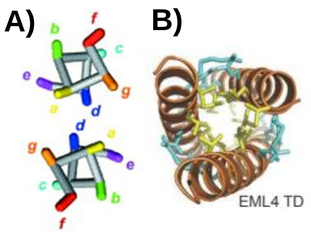
Kinase domains are found at both the **5'** and **3'** location.

- Depends on the cancer or kinase for prevalence.
  - THCA had 94% 3' kinase fusions.

They always require a functional kinase domain to activate and often show a **loss of regulatory domains**.

The fusion partners provide **dimerization domains.** The most common of these are **coiled-coil** domains (see below).

A) **B)**



- They are a series of 2 or more **α-helices**.
- Have a repeating structure of 7 amino acids labelled abcdefg, of which a and d are hydrophobic and form a **hydrophobic core**.

A) Taken from Burkhard et al.(2001). Two stranded coiled-coil.
B) Taken from Richards et al.2015. Trimeric coiled-coil of EML4 TD

Conclusions:

My research has shown that **dimerization domains** provided by the fusion partner genes are the main component in the **ligand independent activation** of the kinase domains. These domains, mainly the very common **coiled-coils**, provide the most promising **therapeutic target**.

Acknowledgements

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References:

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