

ONCOGENIC TRANSCRIPTION FACTORS IN NORMAL AND CANCER STEM CELLS

Using genetic, molecular, cellular and biochemical approaches, we are currently studying the roles of various oncogenic transcription factors in both normal and cancer stem cells.



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Master switch in the stem cells

Many if not all the vital organs in our body are derived from a small number of stem cells, which have the ability to indefinitely regenerate themselves (ie, self-renewal) and give rise to different useful cell types (ie, differentiation). The balance between self-renewal and differentiation is absolutely critical to maintain the constant number and normal function of stem cells. To this end, stem cells have developed a master switch that will automatically adjust the balance between these processes according to the physiological or regenerative needs of our body. After decades of active research, it is now known that this switch is masterminded by a group of proteins called transcription factors which determine the fate of the stem cells.

When the switch goes wrong

Since stem cells play such a critical role in development, it is not difficult to imagine the devastating consequences when the master switch goes wrong. Shifting the balance toward differentiation will lead to stem cell depletion resulting in various degenerative disorders. In contrast, aberrant self-renewal produces abnormal numbers of immature and non-functional stem cells, providing the targets and likely origins for many cancers (see Figure 1). For example, in the haematopoietic system, transcription factors such as MLL are essential for generation and/or maintenance of normal stem cells. Lack of these proteins is not compatible with life. On the other hand, gain-of-function mutations of these transcription factors confer abnormal self-renewal ability to stem/progenitor cells and result in acute leukaemia.

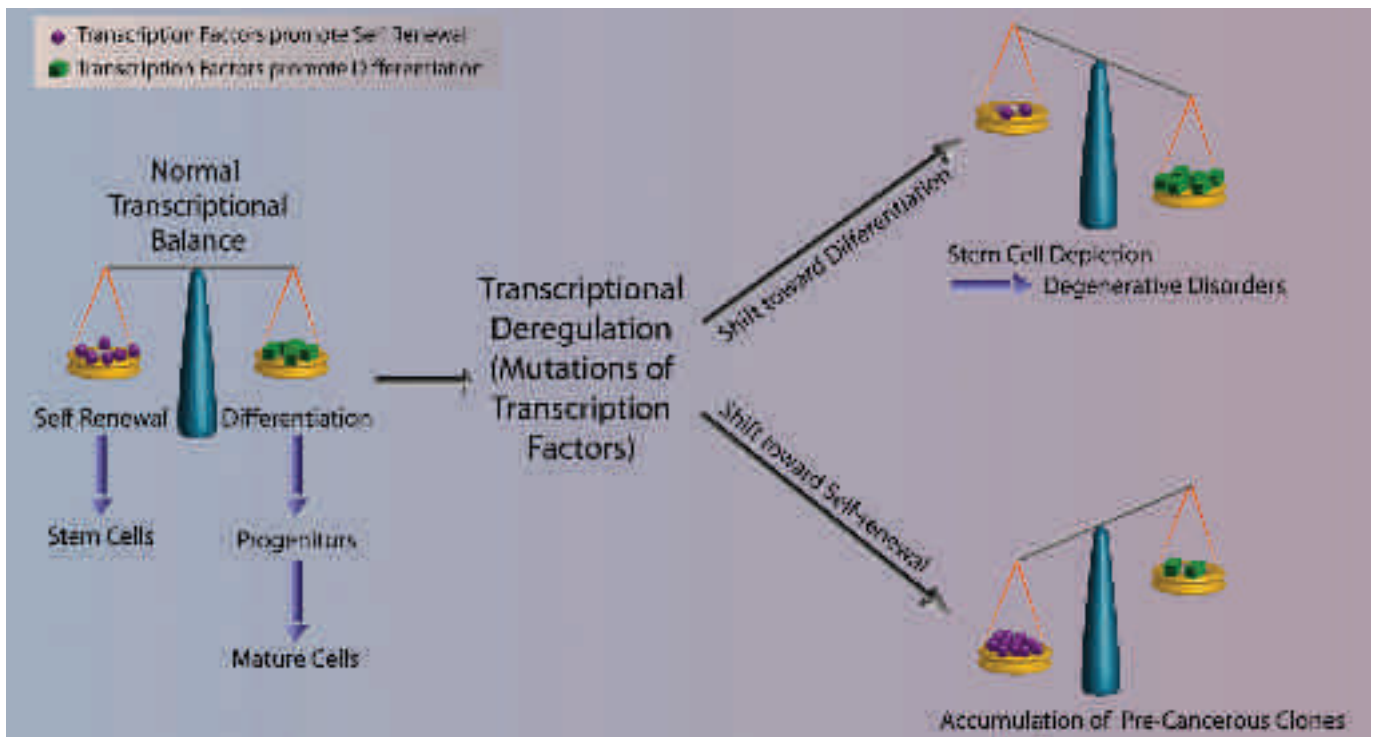


Figure 1: Deregulation of transcriptional balance in stem cells results in cancers and degenerative diseases.

■ Understanding how this master switch works in normal and cancerous settings will not only improve our knowledge of cancer biology but also provide a potential golden therapeutic bullet to target the root of the disease. ■

Finding the faults

A major challenge in identifying the faults in the self-renewal switch is to distinguish the actual critical changes from the overwhelming number of 'noise' mutations found in cancer cells. To this end, our laboratory has developed a method using purified haematopoietic stem cells and progenitors to test and validate the function of various candidate mutations identified in leukaemia patients. Based on this approach, not only have we confirmed the oncogenic property of various leukaemia-associated transcription factors, but we have also dissected the underlying mechanism that abnormally turns on the self-renewal switch. Using oncogenic RAR α and MLL transcription factors found in the majority of acute myeloid leukaemia patients as models, we discovered that a common feature shared by these leukaemia-associated transcription factors is their acquired ability to form illegitimate partnerships (self-association) with each other (see Figure 2). Abnormal self-association has been proposed as a major mechanism for initiating the

oncogenic activity of protein kinases in human cancer (such as BCR-ABL in chronic myeloid leukaemia), but its role in oncogenic transcription factors has not been recognised. To this end, our laboratory has recently shown that aberrant self-association has conferred additional momentum to these transcription factors to shift the balance toward self-renewal and simultaneously inhibit the differentiation process. Moreover, this also seems to be a prevalent mechanism for conversion of critical transcription factors, which normally function in maintaining self-renewal of stem cells, into oncoproteins that drive excessive self-renewal in cancer cells.

On the other hand, for transcription factors to tilt the self-renewal balance, they often need to recruit a number of helper molecules including DNA binding partners and epigenetic regulators to mediate abnormal gene expression (see Figure 2). Basically, the function of these epigenetic mediators is to confer new power to the oncogenic transcription factors, allowing them to obstruct the normal regulation and drive self-renewal to its full speed. Thus, it is crucial to identify the epigenetic regulators being recruited or hijacked by oncogenic transcription factors to shift the self-renewal balance. While it is not difficult to identify candidate proteins that interact with any given transcription factor, the major challenge is to functionally validate the bona fide interacting partners that are essential for the oncogenic process. To this end, we have used various biochemical approaches and identified protein complexes aberrantly recruited by oncogenic MLL transcription factor. Using an oncogenic assay developed in our laboratory,

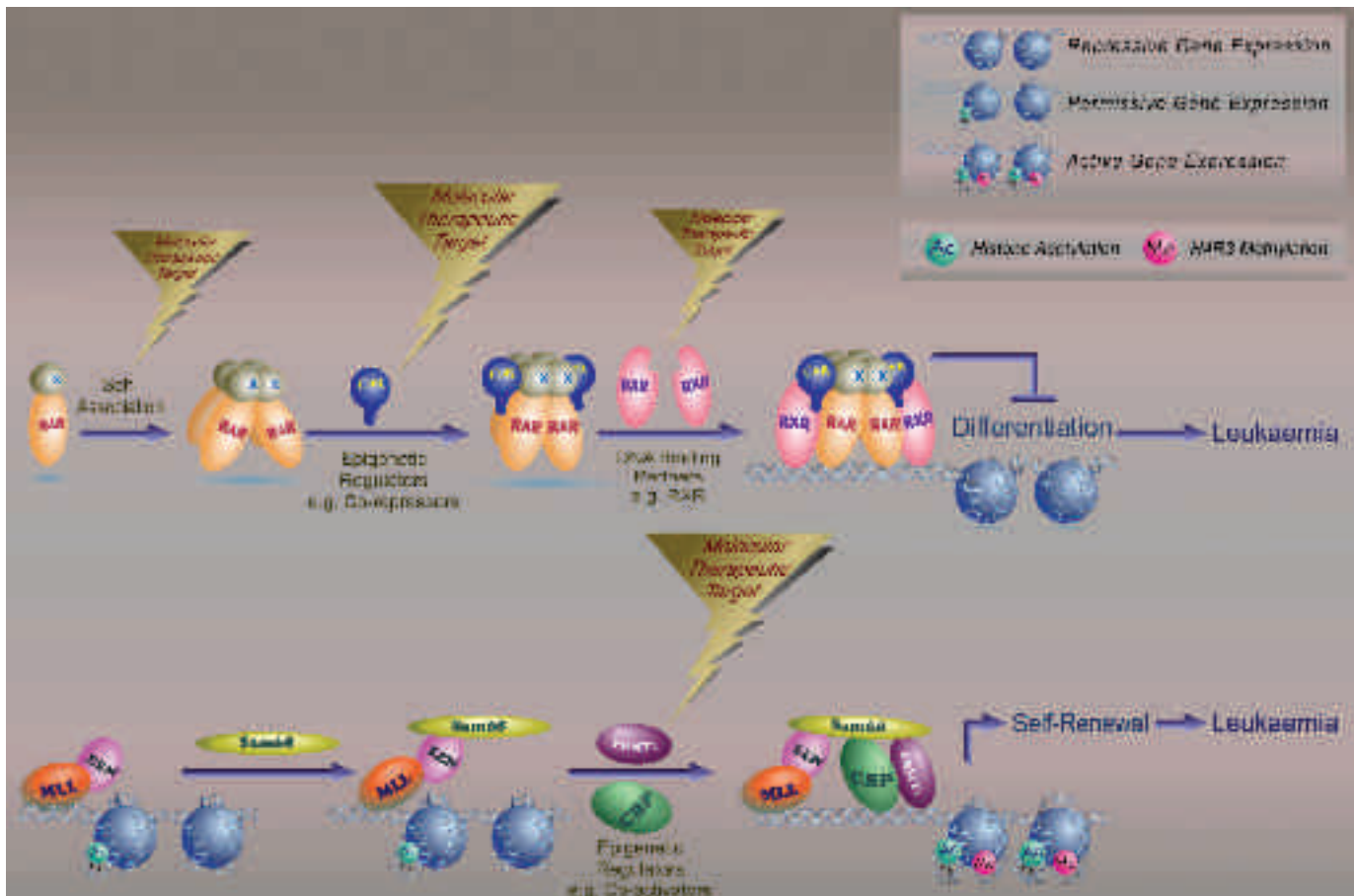


Figure 2: Potential molecular therapeutic targets in acute leukaemia.

we functionally validated the essential roles of various components, including an epigenetic regulator PRMT1, in the complex for mediating the oncogenic process (see Figure 2). This is the first study providing direct evidence showing an essential function and a potential therapeutic value of protein arginine methyltransferases (PRMTs) in cancer.

▣ Finding critical faults that alter the self-renewal process in cancer cells provides us with valuable therapeutic clues. ▣

Fixing the faults and targeting the weakest link

According to our findings, one potential avenue for targeting these oncogenic transcription factors is to disrupt the abnormal self-association property. As a proof-of-principle, we used a specific drug that can interrupt the illegitimate self-association of artificial RAR α fusions (or MLL fusions). Upon drug treatment, transformed cells gradually lost their self-renewal and abnormal growth properties. On the other hand, normal cells remain unaffected. This finding reveals a novel

avenue for selective targeting of the cancer cells induced by oncogenic transcription factors (see Figure 2). In addition, we also recently demonstrated specific inhibition of leukaemic cells by targeting the DNA binding partners (see Figure 2).

While targeting the illegitimate self-association or DNA binding property of transcription factors can inhibit their cancer-inducing activity, the molecules themselves may not be the best therapeutic targets as they usually do not have very well-defined structures and are also too flexible to be inhibited by current small molecule inhibitors. In contrast, a unique feature of the epigenetic regulators is the presence of highly conserved and defined structures (catalytic domains) that are essential for their function to confer new powers to the transcription factors. Because of these rigid and well-defined structures, epigenetic regulators are potentially the weakest links and relatively amenable targets for development of small molecule inhibitors. Thus, targeting critical epigenetic regulators such as PRMT1 that are essential for oncogenic transformation will provide an alternative and effective way to combat cancer cells (see Figure 2).

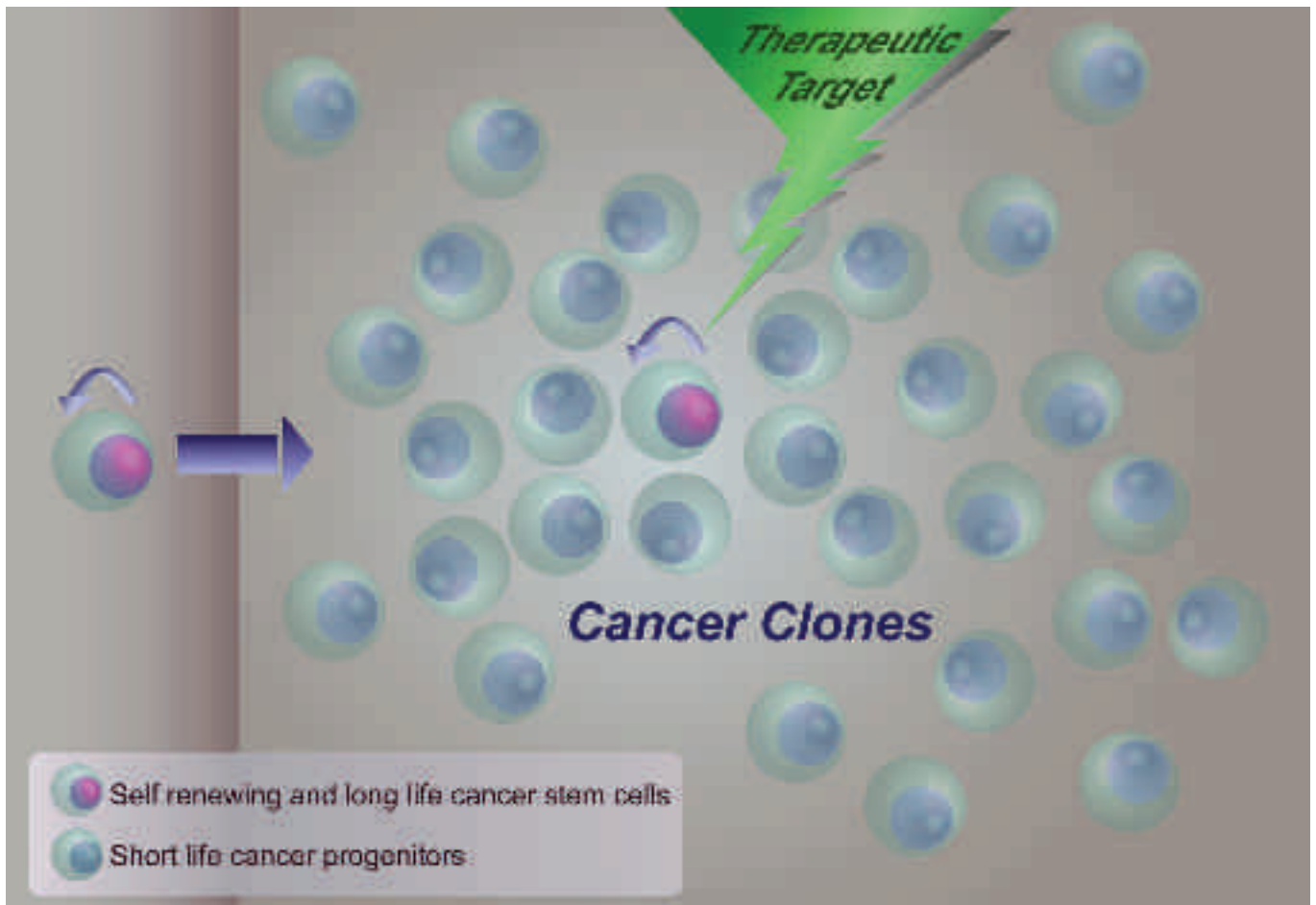


Figure 3: Cancer stem cells as the sources and the critical cellular therapeutic targets for cancers.

■ We plan, with colleagues in the Cancer Research UK Centre for Cancer Therapeutics at The Institute, to explore the possible ways to target this weakest link in cancers. ■

Future direction: Going after the source of cancer clones

It has become clear that most cancers are sustained by a small number of cancer stem cells within the cancer clones, which are probably also responsible for relapse after initial clinical remissions. Therefore, understanding and targeting cancer stem cells is absolutely critical for our fight against cancer (see Figure 3). While the identities and the properties of stem cells in most of the cancers are largely unknown and under vigorous investigation, recent studies have revealed that cancer stem cells at least in leukaemia may have hijacked the similar self-renewal process which operates in normal stem cells. One thing clear to us is that the immortal nature of cancer stem cells is sustained by their unlimited self-renewal ability. If we

can find the transcription factors and/or epigenetic regulators that are essential to promote or maintain the self-renewal of cancer stem cells, it is possible that we can design specific drugs to eliminate this sustaining source of malignant clones.