The Many Lives of CTIP2: From AIDS to Cancer and Cardiac Hypertrophy

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CTIP2 is a key transcriptional regulator involved in numerous physiological functions. Initial works have shown the importance of CTIP2 in the establishment and persistence of HIV latency in microglial cells, the main latent/quiescent viral reservoir in the brain. Recent studies have highlighted the importance of CTIP2 in several other pathologies, such as cardiac hypertrophy and various types of human malignancies. Targeting CTIP2 may therefore constitute a new approach in the treatment of these pathologies.

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Coup-TF interacting protein (Avram et al., 2000) is a Zinc finger transcription factor involved in numerous physiological functions required during development and in adult animal. Germline disruption of CTIP2 is lethal highlighting its importance during development (Wakabayashi et al., 2003). Indeed critical roles of CTIP2 during T cell development (Ikawa et al., 2010; Li et al., 2010), odontogenesis (Golonzhka et al., 2009b), skin development (Golonzhka et al., 2009a), and neuronal development (Arlotta et al., 2005) are now well documented. Initial reports have shown that CTIP2 controls gene expressions by directly binding on a promoter specific sequence (Avram et al., 2002) or indirectly by binding to other promoter-bound transcription factors such as Sp1 (Avram et al., 2000).

We have shown that CTIP2 is a key factor in the establishment and persistence of HIV latency in microglial cells, the main latent/quiescent viral reservoir in the brain. Of note, this HIV-I persistence in the brain has been associated with high level of CTIP2 (Desplats et al., 2013). By deciphering the molecular mechanisms involved in these processes we further showed that CTIP2 might be crucial in the prevention or in the development of other pathologies such as cardiac hypertrophy (HCM) or cancer (Cherrier et al., 2013). Herein we first describe in details the importance of CTIP2 in the establishment and persistence of HIV-I latency in microglial cells. It appears that CTIP2 functions as a critical regulator through different mechanisms. Since CTIP2 is expressed in many cell types and regulates multiple clusters of genes as supported by initial transcriptome analyses in different cell types (Topark-Ngarm et al., 2006; Arlotta et al., 2008), it is not surprising to find CTIP2-sensitive pathways involved in numerous pathologies from cancer and inflammation to cardiac hypertrophy. Interestingly, CTIP2 influences multiple cellular pathways by common molecular mechanisms; raising the possibility to design rational treatments targeting CTIP2.

et al., 2010; Redel et al., 2010; Van Lint et al., 2013). The existence of such reservoirs constitutes today the main obstacle to virus eradication and therefore to a sterilizing cure. Even if this latter might be difficult to reach, we have several reasons to be optimistic to achieve functional cure (Le Douce et al., 2012). This cure aims to mimic what is encountered by patients called “elite controllers” who show very low pool of reservoirs. These patients are able to control viral replication without any treatment, although the mechanism involved is not fully established (Sáez-Cirión and Pancino, 2013). Today, diminution of the pool of the reservoirs constitutes a top research priority of the International AIDS Society (IAS) through the action “Toward an HIV Cure” (Deeks et al., 2012). Research has two main objectives (i) prevention of the constitution of the reservoirs by starting very early the Combination Antiretroviral Therapy (cART) and (ii) reactivation of the latent/quiescent reservoirs in strategies in order to purge reservoirs. Understanding the molecular mechanisms underlying HIV-I latency is therefore crucial. Several levels of

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CTIP2 and AIDS

HIV-I, the causative agent of AIDS, has the property to stay latent/quiescent in different types of reservoirs including the microglial cells, the CNS-resident macrophages (Le Douce

transcription and epigenetic blocks are involved in both establishment and persistence of latency, which prevent reactivation (Van Lint et al., 2013). Previous works from our laboratory have shown that CTIP2 inhibits HIV-1 replication in human microglial (Rohr et al., 2003; Marban et al., 2005). We showed that CTIP2 inhibited HIV-1 gene transcription in these cells by recruiting a chromatin modifying complex (Marban et al., 2007). As demonstrated in T lymphocytes, our work suggests a concomitant recruitment of histone deacetylases HDAC1, HDAC2, and methyltransferase SUV39H1 to the viral promoter by CTIP2 (Fig. 1). We suggested that ordered histone modifications would allow HP1 binding, heterochromatin formation and hence HIV silencing. More recently we showed that CTIP2 in a synergistic manner together with the lysine specific demethylase LSD1 repress HIV-1 transcription and viral expression (Le Douce et al., 2011).

CTIP2 is also able to prevent HIV-1 reactivation through a mechanism that is not well understood. Initial work has shown that CTIP2 represses the late phase of HIV-1 transcription

Fig. 1. Involvement of CTIP2 in AIDS, cancer and cardiac hypertrophy CTIP2 has been described as part of a chromatin remodeling complex, in which it associates with HDAC1, HDAC2, and SUV39H1 (1) and as part of the P-TEFb inactive complex, where it is trapped along with HEXIM1, CTIP2 and the 7sk snRNA (2). Both of those complexes have been shown to orchestrate repression of HIV-1 promoter and genes implicated in both cancer and cardiac hypertrophy. In the case of HIV-1, both complexes appears to bind the promoter through interaction with Sp1 (A,B) and can counter the early phase of viral transcription (C). By recruiting the chromatin modifying complex and furthermore by interacting with LSD1/COMPASS/Set1, CTIP2 induces heterochromatin formation through modification of the epigenetic code and thus establishes latency (A). In the mean time, CTIP2 is also able to limit reactivation event by recruiting the inactive form of P-TEFb on the promoter and to slow down transcriptional activity sufficiently to revert back to latency during the early phase of transcription (B). In favorable conditions, the viral genome is transcribed during the early phase and lead to the production of the first viral proteins such as TAT (C). As opposed to the P-TEFb inactive complex, P-TEFb also exists as a free active form (3), which is recruited by TAT at the TAR element during the late phase of viral transcription (D). However CTIP2 is also able to hijack the P-TEFb/TAT complex, thus preventing transcription and reactivation events (E). CTIP2 has also been linked to cardiac hypertrophy by down regulating clusters of P-TEFb-sensitive genes implicated in this pathology. For instance CTIP2 favors P-TEFb inactive form recruitment through still undetermined transcription factor (TF) (F). Even though evidence of CTIP2-mediated recruitment of inactive P-TEFb onto tumor suppressor gene has not emerged yet, CTIP2 has already been shown to shut down expression of the p21 gene, which could be linked to cancer development. The CTIP2 chromatin remodeling is anchored to sp1 onto the p21 gene promoter (G) and, in the manner of what has been described in HIV-1 latency establishment, leads to the heterochromatin formation in the vicinity of this promoter.

which is Tat-dependant (Rohr et al., 2003). This crucial step relies on the recruitment and activation of the P-TEFb elongation factor by Tat. P-TEFb is composed of a regulatory subunit CyclinT1 and a catalytic subunit CDK9 whose kinase activity is involved in the Ser2 phosphorylation of the carboxyl terminal end of the RNA polymerase II and in the phosphorylation of the negative transcriptional elongation factor NELF and DSIF. Subsequent to phosphorylation, the RNA pol II processivity drastically increases which leads to an efficient transcription of genes (Bres et al., 2008). One current model postulates that Tat recruits first the inactive P-TEFb-7SKsnRNP complex to the Sp1 binding sites of the HIV-1 promoter and in a second step Tat transfers P-TEFb to the TAR on the nascent transcript, which activates its catalytic subunit CDK9 (Sobhian et al., 2010). We have shown in a recent paper that CTIP2 is associated with an inactive P-TEFb, which is found in a multiprotein complex including 7SK snRNA and HEXIM1 anchored at cellular gene promoters (Fig. 1) (Cherrier et al., 2013). Of note, CTIP2 significantly repressed CDK9 kinase activity in this inactive complex and together with HEXIM1 thus inhibited P-TEFb functions. How Tat recruits PTEF-b on TAR and how Tat facilitates P-TEFb activation is not fully understood. Recent works from Benkirane's lab showed that Tat exists in two P-TEFb-associated complexes (Sobhian et al., 2010). Tat-com1 includes MLL fusion partners and the PAF1 complex and potentiates Tat-mediated transactivation, while Tat-com2 contains P-TEFb, the 7SK snRNA, LARP7 and MEPCE and represses Tat functions. Our preliminaries results suggest that CTIP2 associates with both PAF1 and LARP7. The influence of CTIP2 in tat-associated complexes and the mechanism of Tat-induced CDK9 kinase activation are not known and will need further investigations. A conformational change in the structure of CDK9 recruited by Tat on the TAR together or associated with the release of kinase inhibitors (CTIP2 and/or HEXIM1) from the snRNP might be involved in the recovery of its kinase activity.

In addition to its direct influence on the HIV-1 promoter, CTIP2 has even a more pleiotropic action through the control of cellular genes of importance for the virus. Among these factors, the cellular cyclin-dependent kinase inhibitor CDKN1A/p21^{waf} has been described to favor HIV-1 gene transcription in the monocyte-macrophage lineage. Recruited to the p21 promoter, CTIP2 silences p21 gene transcription by inducing epigenetic modifications as described above for the HIV-1 promoter (Fig. 1) (Cherrier et al., 2009). This effect indirectly favors HIV-1 latency since activation of p21 gene stimulates viral expression in macrophages (Vazquez et al., 2005). Moreover, CTIP2 counteracts HIV-1 Vpr protein which is required for p21 expression. We therefore suggested that CTIP2 might generate a cellular environment disfavoring viral reactivation and thus favoring HIV-1 latency.

From AIDS to Cancer and HCM

Since CTIP2 is an inhibitor of P-TEFb it is not surprising that CTIP2 is involved in several P-TEFb dependent pathologies such as cancer (Wang and Fischer, 2008) and HCM (McKinsey and Kass, 2007; Harvey and Leinwand, 2011). Indeed CTIP2 has been described as a tumor suppressor gene (Kamimura et al., 2007; Gutierrez et al., 2011) or an oncogene (Oshiro et al., 2006), and has been implicated in hematological malignancies (Huang et al., 2012; Kadoch et al., 2013) and Ewing sarcoma (Wiles et al., 2013). Around 10–16% of Human T-Acute lymphoblastic leukemia (T-ALL) were associated with mutations or deletions of CTIP2 (BCL11b) gene (Kominami, 2012). Among P-TEFb sensitive genes which might be involved in cancer development we found the gene encoding the cyclin-dependant kinase inhibitors p21 (Qian et al., 2013). Interestingly CTIP2 repressed p21 gene expression by inducing

a heterochromatin environment at its promoter (Cherrier et al., 2009) and by inhibiting P-TEFb functions (Fig. 1). The recent genome-wide analysis of gene co-regulated by CTIP2 and a dominant negative mutant of CDK9 (dnCDK9) showed that 25% of genes whose expression were altered by CTIP2 were also found to be sensitive to dnCDK9. Interestingly around 80% of genes regulated by CTIP2 were consistently regulated by dnCDK9 which argue in favor of down regulations of P-TEFb sensitive genes through inhibition of the CDK9 kinase activity (Cherrier et al., 2013). It is noteworthy that CTIP2 is also involved in inflammation initiation (Cismasiu et al., 2009; Wang et al., 2012) which is a key risk factor for cancer. The transcriptome analysis is in accordance with this hypothesis, since CTIP2 has been shown to impact the NF- κ B/NFAT pathway. Indeed these two pathways are involved in inflammatory processes (Fric et al., 2012; Oh and Ghosh, 2013) which subsequently may lead to cancer including leukemia and solid tumors (Medyouf and Ghysdael, 2008; Kipanyula et al., 2013). Very interestingly both CTIP2 and the calcineurin/NFAT signaling pathways are involved in the progression of malignancies such as T-ALL leukemia which further strengthen the idea that CTIP2 is able to modulate the calcineurin/NFAT signaling pathways (Medyouf and Ghysdael, 2008). A better comprehension of the molecular regulation of these two signaling pathways by CTIP2 should be important in the design of new therapeutic targets against the development of inflammation and/or cancer.

Finally we showed that CTIP2 is also involved in pathologies such as HCM which is already a well described P-TEFb sensitive disease (Harvey and Leinwand, 2011). A comparison of gene expression profiles from HCM mice and those obtained from CTIP2 knockdown and CDK9 overexpression studies showed that 50% of the CDK9-sensitive genes are also CTIP2-sensitive. The gene encoding the sarcomeric β -myosin heavy chain protein, which is considered as a hypertrophic marker (Passier et al., 2000), is down regulated by both CTIP2 over-expression and through inhibition of the CDK9 kinase. We notably showed that CTIP2 is anchored to the β -myosin heavy chain gene promoter and is associated with the inactive P-TEFb complex (Fig. 1). Our results strongly suggest that CTIP2 regulates several pathways involved in the development of HCM such as the MAPK, the Ca^{++} /calmodulin, the NF- κ B/NFAT and the PI3K/Akt pathways (Fig. 2). Of note, cardiac hypertrophy, which is a major predictor of heart failure, develops through responses from cardiomyocytes to mechanical and neurohormonal stimuli. It is now well described that these responses involved several intracellular signaling pathways including the MAPK, the Ca^{++} /calmodulin, the NF- κ B/NFAT and the PI3K/Akt pathways (Rohini et al., 2010). Remarkably all these signaling pathways facilitate the recruitment of P-TEFb on target genes involved in HCM to stimulate their transcription (Contreras et al., 2007; Espinoza-Derout et al., 2007; Chen et al., 2008; Fujita et al., 2008; Liu et al., 2012; Ruppert et al., 2013). CTIP2 could modulate these four signaling pathways by inhibiting CDK9 kinase activity (Fig. 2) and thus prevent the development of HCM. Highlighting the importance of CTIP2 in the regulation of these signaling pathways might help to devise new therapies in order to prevent, reduce and/or reverse HCM development. Targeting these signaling pathways has already lead to the development of small-molecule therapies for HCM, while several agents are ready for clinical testing (McKinsey and Kass, 2007).

Therapeutic Implications

There are now substantial evidences that multiple pathologies rely on deregulations of CTIP2-sensitive pathways. Therefore CTIP2 or its associated complexes constitute promising targets for therapeutic intervention. Improving T-acute

Fig. 2. CTIP2 could neutralize akt-, Nf- κ B/NFAT-, Ca^{2+} /calmodulin- and MPAK-signaling pathway-based cardiac hypertrophy. Multiple signaling pathways have been linked to modulation of genes leading to adaptive or maladaptive cardiac myocyte hypertrophy. P-TEFb appears to be a common downstream component of those signal transduction pathways, while being a key factor in gene transcription. CTIP2 by counteracting the active form of P-TEFb could hence offset the effect of such intracellular responses and prevent cardiac hypertrophy to arise.

lymphoblastic leukemia (T-ALL) treatment strategies will need further investigations since it is not well understood whether CTIP2 contributes negatively or positively. Strategies based on CTIP2 silencing by using RNA interference in T-ALL have been proposed since down regulation of CTIP2 leads to apoptosis of malignant cells but not normal mature cells (Grabarczyk et al., 2007; Huang et al., 2011). In addition, targeting CTIP2-associated enzyme, SUV39H1 by chaetocin has been described as a potent treatment against T-ALL (Chaib et al., 2012). It is of note that cross talk between two signaling pathways regulated by CTIP2, that is, PI3K/Akt and NF- κ B, are involved in several malignancies (Hussain et al., 2012). A synergetic targeting of these two pathways might be expected and would need further investigations. However we have to be aware that many drugs currently used in cancer therapy have severe adverse effects especially by promoting cardiotoxicity (Albini et al., 2010; Raschi and De Ponti, 2012). Targeting CTIP2 or CTIP2-associated enzymes might work in cancer therapy but clinical studies showing absence or reduced side effects are needed before their clinical use. Indeed it is well documented that numerous drugs targeting signaling pathways modulated by CTIP2 have adverse affects such as cardiotoxicity. Agents for molecular targets such as mTOR belonging to the PI3K/Akt signaling pathway or HDAC belonging to Ca^{++} /calmodulin signaling pathway have been associated with cardiovascular toxicity including hypertension, heart failure and venous thromboembolism (Svoboda et al., 2012). Balance of benefits and detrimental effects of strategies based on CTIP2

silencing will therefore need further studies before its clinical use.

Identifying CTIP2 functions in the establishment and the persistence of latency have profound therapeutic implications through strategies aiming to purge/reduce the reservoirs. Indeed viral reactivation combined with intensive HAART might lead to decrease the size of these reservoirs enabling the immune system of patients to control HIV. Several CTIP2-associated proteins involved in heterochromatin formation have been identified and targeted to allow reactivation. Several potential interesting candidates have emerged such as histone deacetylase (HDAC) (Marban et al., 2007) and histone methyltransferase (Marban et al., 2007; du Chene et al., 2007; Imai et al., 2010). Several HDAC inhibitors such as vorinostat (Archin et al., 2009) and romidepsin (Geleziunas et al., 2012; Van Lint et al., 2013) are indeed very potent agents that induce HIV-I latency. Interestingly these agents have already been licensed or approved by FDA in treatment of malignancies and seem to be well tolerated by humans. Since several mechanisms of latency have been described (DNA methylation, histone acetylation, histone methylation, P-TEFb inhibition, etc.) we might expect a synergistic action on HIV reactivation with a combination of different HIV-I inducers. Indeed, use of combination of HDAC inhibitors and histone methyltransferase inhibitors is very promising since it has been shown that their combination allows higher reactivation than these compounds alone in CD4⁺ T cell cultures from HIV-I positive cART-treated patients with undetectable viral load (Bouchat et al., 2012). Since P-TEFb is needed for viral expression, combining of P-TEFb activation with HDAC and HMT inhibitions might even show a higher efficiency of viral reactivation. Another expected advantage of the use of several compounds in combination is that HIV reactivation might be achieved by using lower concentrations of each inducer when taken together. However recent findings suggest that pharmacological reactivation of latent HIV-I is not enough to cause infected cell death, especially in cells from the monocyte-macrophage lineage which are very resistant to the cytopathic effects of the virus (Shan et al., 2012). Clearing of reactivated reservoirs might be achieved by different immunotherapeutic approaches that increase cytolytic T lymphocytes (Vanham and Van Gulck, 2012). A strategy based on CTIP2 silencing by using RNA interference might be tested since down regulation of CTIP2 might lead both to HIV-I reactivation and to cell death through apoptosis (Abbas and Herbein, 2013). Finally a better understanding of the impact of CTIP2 on the P-TEFb-mediated control of transcription elongation which appears to be a dynamic and fine-tuned process will undoubtedly allow designing new pharmacological drugs for the treatment of P-TEFb-dependent pathologies.

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