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Epigenetic programming of cancer-related inflammation byncRNA rheostat: Impact on tumor directed immune therapies

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Summary

Accumulating evidences demonstrate that the host genome's epigenetic modificationsare essential for living organisms to adapt extreme conditions.DNA methylation, covalent modifications of histone, andinter-association of non-coding RNAs facilitate the cellular manifestation ofepigenetic changes in the genome. Out of various factors involved in the epigenetic programming of the host, miRNA (microRNA) and LncRNA (Long non-coding RNA) are new generationnon-coding molecules that influence a variety of cellular processes like immunity, cellular differentiation, and tumor development. During tumor development, temporal changes in miRNA/LncRNA rheostat influence sterile inflammatory responses accompanied by the changes in the carcinogenic signalling in the host. At the cellular level, this is manifested by the up-regulation of Inflammasome and inflammatory pathways, which promotes cancer-related inflammation. In view of this, we discuss the potential of lncRNA and miRNA directed interventions in regulating inflammation and tumor development in the host.

Keywords: Cancer related Inflammation; miRNA; LncRNA; Epigenetics, immune polarization

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Highlights

- IL-1β and NF-KBsignalling pathways are crucial regulators of Cancer-related inflammation.
- Non-coding RNAs like *FAL1*, *PVT1*, and *miR-15/16* promote carcinogenesis.
- *miR-511-3p*, *miR-33*, and *miRNA-19a-3p*potentially modulate the polarization of TAMs and regulate tumorigenesis.
- Silencing of *MALAT1* foster anti-cancer immunity by controlling M2 TAM polarization.
- *INCR1* increases susceptibility of the Cancer cells to CD8+ cytotoxic T lymphocytes and afforded help toCAR-T cell therapy.

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Inflammation: Bread and butter of Cancer

Inflammation is a non-specific host defence against tumor and is essential for both control and progression of cancer. This is manifested with the changes in Th1/2 (helper T cell 1/2) bias in patients' tumor micromilieu, which ultimately influences host immunity either in favour or against growing tumor mass in patients. Immunogenic inflammation is pre-requisite for the host in controlling cancer growth mainly via tweaking M1 TAM (tumor associated macrophages), which promotes the immunogenic death of tumor cells by expression of interleukins*IL-2*, *IL-12* and *IFN* (Interferon) (Waldmann, 2018). On the other hand, when immunogenic inflammation persists, it becomes chronic and refractory where, it supports the growth of tumor mass by promoting in situ programming of tumor infiltrating M1 TAM towards M2 TAM, which is tropical and supports tumor cells development by promoting secretion of several proteases, cytokines and angiogenic growth factors (Yahaya et al., 2019)(Balahura et al., 2020).

Chronic inflammation is characterized by high levels of ROS (reactive oxygen species), which in concert with locally produced RNI (reactive nitrogen intermediates), promote DNA damage and trigger carcinogenesis(Broderick et al., 2015). Further, this chronic state is characterized by enhanced infiltration of immune effectorslike TAMs and T-regs (regulatory T cells), which secretecopious levels ofpro-inflammatory cytokines such as IL-1β, TNF-α (tumor necrosis factor alpha) andROS/RNS (reactive nitrogen species), which triggers fibrosis, excessive tissue damage,and tumorigenesis(Chiba et al., 2012).

Out of several factors which are present in tumor micromilieu,Th1 cytokines like IL-1β and IL-18 are major inflammatory cytokines which regulate cancer cell fate.IL-1β is responsible for Th17 programming ofimmune cells(Dinarello, 2009)[(Yasuda et al.,

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2019), which is decisive for the development of tumor. Typical Th17 response factors like TNF-α and IL-1 activate non-canonical NF-KB (nuclear factor kappa light chain enhancer of activated B cells) landscapewhich further enhances the secretion of IL-6, TNF-α, VEGF (vascular endothelial growth factor) and expression of *iNOS* (inducible nitric oxide synthase), that promotesinflammation, angiogenesis and tumor development(Dunn et al., 2012).However, in this line,the anti-cancer role of IL-18 is controversial; IL-18 induces the expression of *IFN-γ*, which is the central cytokine ofTh1 effector response and is decisive for immune-mediated destruction ofmany cancers (Esmailbeig and Ghaderi, 2017) by phagocytes like M1 TAM**.** Because of suchregulatory nature of Th1 responses, theyare explored as potential targets for cancer-directed interventions. Many therapeutics like Anakinra, which inhibits IL-1 receptor [11], and simvastatin [12], which downregulates the expression of *IL-1β&IL-18*, have beensuccessful incontrollingboth migration and proliferation of cancerous cells.Similarly, polydatin mediated tweaking of canonical *NF-KB* pathways has effectively controlled tumor burden in animal studies(Zou et al., 2018).

A deeper analysis of molecular events has suggested inflammasomes as critical regulators of immunogenic inflammation in various infection-related aberrant immune pathologies. The Inflammasome is the bunch of intracellular proteins that get activated in response to PAMP (pathogen-associated molecular pattern) or DAMP (danger-associated molecular pattern) signalling and help maintain the homeostasis of the infected/damaged tissue in various stress conditions. NLRP12 (NOD-, LRR- and pyrin domain-containing protein 12) is one of the major components ofthe Inflammasome,which negatively regulate the canonical NF-KB signalling pathway, control overt inflammation in hematopoietic and non-hematopoietic compartments (Allen et al., 2012). NLRP4 is expressed in many tissues and acts as a negative

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regulator of *type-I IFN* signalling and Autophagy (Jounai et al., 2011). It also inhibits IL-1β and TNF-α mediated *NF-κB* activation/signalling (Eibl et al., 2012) and is essential in mediating immune response against viral infections and cancer. In this direction, NLRP3 activation induces caspase-1 expression,which is decisive forthe secretion of IL-1β & IL-18 in active forms(Xue et al., 2019). These few examples corroborate the regulatory role of Inflammasome over immunogenic inflammation. They suggest that these pathways may be involved in the polarization of either tumor infiltrating or intra-tumoral populations of M2-TAM, N2-TAN (tumor associated neutrophils) and T-regs.

Further, Th1 effector cells like M1macrophages,NK (natural killer) cells and CD8+ T cells are essential prerequisites of host immunity to keep the tumor growth/burden at bay. On the other hand, Th2 effector cells like M2-TAMs/ N2-TANs and MDSCs (myeloid-derived suppressor cells) inhibit the growth of CD8+ T cells by establishing an immunosuppressive/pro-tumorigenic environment and escort tumor cells for their colonization, metastasis and growth. Most intriguingly, Th17 cells, being double edge components of immunity, secrete factors like IL-17F, IL-17A, IL-22 and IL-21 and are both pro-tumorigenic and anti-tumorigenic. Among various tumor-associated immune cells, TAMproduces high levels of IL-1β and promote the differentiation of CD25+Tregs into *RoRγ*+Th17cells(Kryczek et al., 2009). Once differentiated, Th17 cellsrecruit other cell types such as iDCs (induced dendritic cells), iNK cells (induced natural killer cells), CTLs (cytotoxic T lymphocytes), TNF+CD4+T cells and contribute inestablishing a tumorigenic environment. Several in-vitro studies have reported that some of the components of Th17 response like,*IL-6, IL-17,TGF-b*(transforming growth factor beta),*IL-23p19,* and *Wnt*signalling are well known

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epigenetic programmers ofbothhost and tumor cells (Chiba et al., 2012; Maiuri and O'Hagan, 2016), and are believed to contribute in tumorigenesis.

Non-coding RNAs: switch between inflammationcancer

As described above, acute inflammation often becomes chronic,especially in cancer or latent infection and work against the host. This is due to epigenetic changes in the host genome (Fardi et al., 2018). Thesechanges are instrumental in the plasticity of immune response and disease progression. 98% of the entire genome comprises non-coding RNAs of various lengths [20], which do not code for protein and are transcribed and released in the cytoplasm as an untranslated molecular contaminant. These get accumulated in the cancer patients, where theyplay an important role in regulating cell functions and cancer. So far, two major categories of such oligos have been identified in the host. One of them is miRNAs, which are short non-coding RNA that mediates mRNA degradation and repression of post-transcriptional mechanism epigenetically. Another category is known as LncRNAs which regulate gene expression by interacting with DNA, mRNA & protein (Poli et al., 2020). miRNAs can regulate and control the expression of several coding and non-coding genes, including harmful oncogenic genes such as*c-Myc*(cellular Myc)*, EGFR*(epidermal growth factor receptor)*, RAS*(Rat sarcoma) and some TSGs (tumor suppressor genes), including *BRCA1*(breast cancer type 1)*, PTEN*(Phosphatase and Tensin Homolog deleted on Chromosome 10) and *TP53*(tumor protein p53) (Slack and Chinnaiyan, 2019).

Non-coding RNAs supportcancer development in many ways, such as by (i) genetic alteration in the gene which codes for ncRNA (non-coding RNA)(Calin et al., 2002); (ii) amplification in chromosomal regions containing oncogenic ncRNA as seen

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inLncRNAs like*FAL1* (focally amplified LncRNA on chromosome 1)(Hu et al., 2014) and *PVT1* (plasmacytoma variant translocation 1)(Tseng et al., 2014); (iii) stabilization of SNPs (single nucleotide polymorphisms) corresponding to LncRNAs *H19*(Yuan et al., 2018) and *CCAT2* (colon cancer-associated transcript-2)(Ling et al., 2013); (iv) inducing point mutations in the promoter region of ncRNAs like *RMRP*(ribonuclease mitochondrial RNA processing) and *NEAT1*(nuclear enriched abundant transcript 1) in breast cancer (Rheinbay et al., 2017); (v) dysregulating the synthesis of an enzyme such as Drosha and Dicer which are involved in the processing of miRNA (Rupaimoole and Slack, 2017). Besides this, some LncRNA like *NKILA*(NF-KappaB Interacting LncRNA) has dual roles, *NKILA*can negatively regulate canonical *NF-KB* signalling, immunogenic inflammation, and cancer. In contrast, *NKILA* is also capable of promoting tumor development by mitigating T_H1 response and CTL inactivation (Huang et al., 2018) and promote tumor development. Given this, temporal regulation of ncRNAs in the host is believed to control tumor development or their sensitivity for tumor directed interventionsthrough transcriptional, post-transcriptional and epigenetic processes (Adams et al., 2014; Anastasiadou et al., 2018; Rupaimoole and Slack, 2017). Further an overview of role of non-coding RNAs in controlling and promoting cancer development are discussed in**Table 1**&**2** and depicted in **Figure 1**

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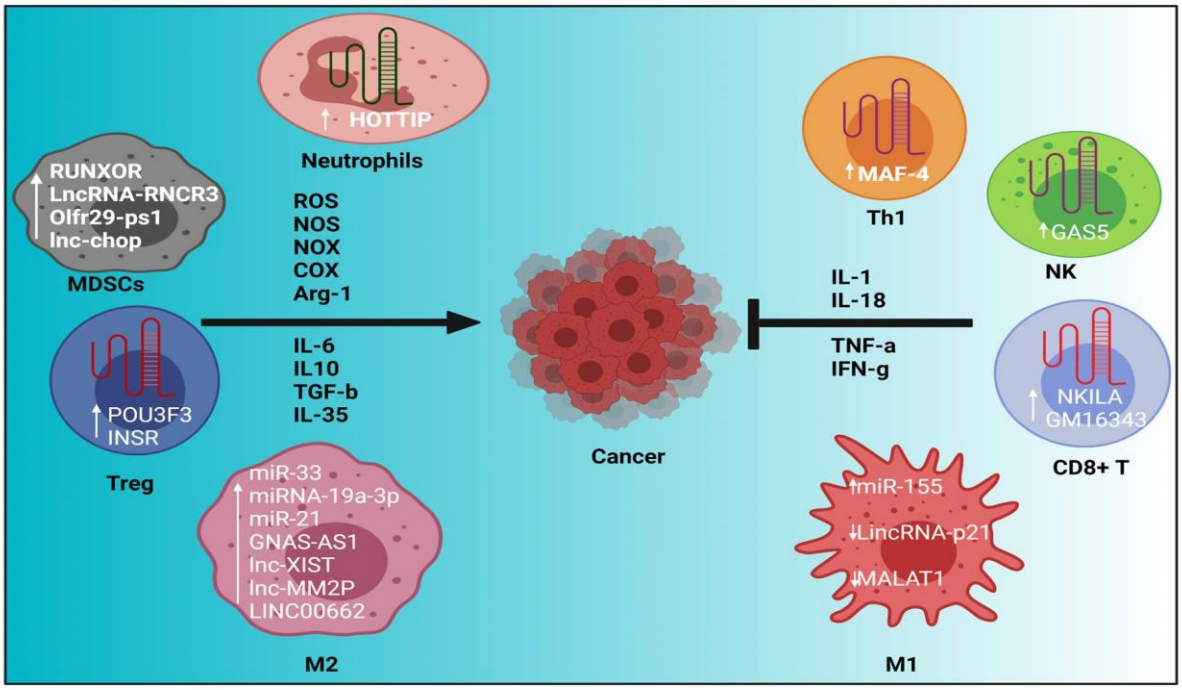

Figure 1. Non-coding RNAs regulate the immune cells/inflammation and cancer progression.1. Pro-cancer non-coding RNA promote M2/Th2 polarisation/response and support tumor progression. **2.** Anti-cancer non coding RNA promote M1/Th1 polarisation/response and controls tumor progression.

MiRNAs: Internal bottlenecks

miRNAs are non-coding molecules that are detrimental in chronic inflammation for promoting cancer in the host. For example, *miRNA-223*blocks IL-1β production by blocking 3'-UTR of *NLRP3* mRNA and suppresses *NF-KB* signalling for the progression of squamous cell carcinoma (Yan et al., 2019b). In contrast, the expression of *miR-133a-1* in the host increases the activity of NLRP3/caspase-1 and active IL-1β production (Bandyopadhyay et al., 2013). Whereas, *miR-21* deficiency can inhibit NLRP3 activation and IL-1β & caspase-1 expression (Xue et al., 2019), and help host immunity in controlling tumor growth more effectively.

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Cancer cells rely upon many signalling events that enable them to evade immune attacks mainly by subverting immunogenic inflammation that is hostile to their existence. In this context, non-canonicalNF-kB signalling is known to trigger tumorigenesis (Chew et al., 2018), which is primarily manifested by *miR-146*which targets*IRAK1*(Interleukin-1 receptor-associated kinase 1) and *TRAF* (TNF receptor-related factor) and in-turn controls *NF-kB*(Taganov et al., 2006) signalling landscape. These studies emphasize the importance of miRNA-mediated post-transcriptional regulation of pro-cancerous signalling. Besides the *NF-KB* pathway, the *JAK-STAT*(Janus kinase/signal transducers and activators of transcription) pathway is another fundamental carcinogenic pathway which isregulatedbyncRNA. *miR-135*(Wu et al., 2012), *miR-145*(Gregersen et al., 2010),*miR-221/222*(Zhang et al., 2010),*let-7*(lethal-7) (Wang et al., 2010b),and *miR124*(Koukos et al., 2013) are some common examples of miRNA which regulate *STAT1* and influence carcinogenesisin several cancer cell lines including HepG2 (human liver cancer cell line) and COLO205 (human colon carcinoma).

miR-155 is well known to promote type-I IFN signalling, which is pro cancerous in nature.Increased expression and stability of *miR-155* in hematopoietic tumors (Wang et al., 2010a) is well-documented evidence that this miRNA indeed is cardinal for tumorigenesis. Interestingly, this miRNA inhibits IFN gamma signalling and promotes M2 polarization of tumor infiltrating M1 effector macrophages in theTME (tumor microenvironment). *miR-511-3p*, on the contrary, inhibits tumor growth mainly by aborting M2 polarization of TAM by downregulating the pro-tumoral gene signature of TAMs (Squadrito et al., 2012), thus represent a plausible target of cancer-directed immune directed therapies.Most intriguingly,this paradoxical signalling of miRNA suggests that one or more miRNA can promote or inhibit tumor development by

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adjusting the yin and yang of fundamental immune pathways. Few more examples in this direction are,*miR-33*,*miRNA-19a-3p*(Ouimet et al., 2015), and *mir-21*(Caescu et al., 2015)which promote M2 polarization and cancer progression. These examples indicate that miRNA is a penultimate target for adjusting host signalling pathways required for curtailing the fate of tumors in the host.

In the same line, other than macrophages, miRNAsareimportant for orchestratingNK cell immunity in the host. Set of microRNAs including*miR-122*,*miR-21*, *miR-15b*, and *miR-155* are known to activate naiveNK cells, promote their differentiation, and repress tumor development in mice models(He et al., 2013). Inhibition of *LncRNA GAS5*(Growth Arrest Specific 5)is deleterious for NK cellsmediated ADCC (Antibody-dependent cellular cytotoxicity), whereas its overexpression increases secretion of IFN-γ and promotes/rescues ADCC, this is accomplished by the destabilization of *miR544*(Fang et al., 2019). Few lines of evidence suggest that ncRNAs like *miR-17/92*(Shen et al., 2017)&*miR-20a*(Xie et al., 2014) can inhibit the NK cell activation and ADCC. Similarly,*miR-146a*(Paik et al., 2011), *miR-150*(Watanabe et al., 2011), and *miR-30b*(Ng et al., 2011) suppress viability of NK/T cells and promotetumor development in the host, suggesting that targeting these miRNAwould be decisive for rescuing NK cells activity.

Apart from innate cells, miRNAs also modulate adaptive/T-cell responses by regulating T-regs and IFN-γ production, affecting immune checkpoints and many more. Some examples in this direction include *miR-21*, whichcontrol the population of *CCR6*+ Tregs *in situ*via*PTEN/AKT*(Protein kinase B) pathway (Hu et al., 2015);and *miR-23a*which suppress BLIPM-1 (B lymphocyte-induced maturation protein-1) activity and tumor-induced immune polarization of infiltrating T cells(Lin et al., 2014), thus contributing to anti-tumor immunity.

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LncRNAand immune escape:roller-coaster paradigm

LncRNA can regulate some of the above mentioned miRNAs and modulate inflammation-related genes/transcripts both positively and negatively.In this line, certain LncRNAs like*COX2*(cyclooxygenase-2), *PACER*(p50-associated cyclooxygenase-2 extragenic RNA), *AS-IL1a*(antisense noncoding RNA in IL-1a locus), *IL1b-RBT46*, and *IL1b-eRNA* are important for TLR4signaling in macrophages(Castellanos-Rubio et al., 2016; Chan et al., 2015; Ilott et al., 2015; Krawczyk and Emerson, 2014). Similarly, *NKILA* is up-regulated in*IL-1b* and *TNF-a* mediated pathways and enhances the adaptive immune system's inflammation/anti-cancer response [71].In contrast, *LncRNA-EPS* (erythroid pro-survival)is downregulated upon TLR signaling via the NF-KB axis and restrains inflammation (Atianand et al., 2016) via the NF-kB pathway. *THRIL* (TNF and HNRNPLrelated immunoregulatory lincRNA) is activated upon TLR2 activation and induces TNF-a secretion (Li et al., 2014). Activation of TLRs induces *COX2*, which is primarily required for transcription of inflammatory genes (Hu et al., 2016).

LncRNA-EPS is also known to maintain resting phenotype in macrophages by keeping down the expression of the IR (immune response) genes in naïve macrophages. *LncRNA-EPS* knockdown/deficient animals display a naturally high level of inflammatory cytokines (Atianand et al., 2016). Together with *NKILA*, it is now evident that ncRNA are immunological chaperons and govern the plasticity of macrophages. Some LncRNA arevery elastic and having a dual impact on the inflammatory programming of the host. CD11b+ macrophages from animals depleted of*COX2*lead to constitutively activated IFN stimulated genes and inhibited *IL-6*mainly

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via hnRNPA2/B1 (heterogeneous ribonucleoprotein)and hnRNPA/B, which regulates IR genes transcription (Hu et al., 2016).

Insensitivity toward immune stimuli is one of the key characteristics of a variety of malignant/aggressive cancers. This is the main bottleneck and a major focus of improving existing cancer-directed Immunotherapies. A compromised antigen presentation,T cell exhaustion, higher frequency of Treg, MDSCs, and TAMs are the key feature that enablestumor cells to subvertimmune attack, confer immune evasion and impart therapy resistance in solid, angiogenic and aggressive tumors. As discussed in previous sections,ncRNA areassociated with cancer-related sterile inflammation. We here propose that ncRNA indeed represents prominent candidates for breaking innate resistance of tumors for treatment regimen. *LETHE* and *NEST* (nettoie Salmonella pas Theiler's) are two well-known examples of LncRNAthat are probably responsible for the resistance of tumor cells. Mechanistically, *LETHE* is a negative feedback regulator of TNF-a-driven canonical *NF-KB*signaling, secretion of IL-6 and IL-8 [75]. Whereas, *NEST* supports the expression of *IFN-g*and related immunogenic signature and sensitivity of *CD8*+T cells (Gomez et al., 2013) for tumors.

LncRNA like *NEAT1* (nuclear paraspeckle assembly transcript 1)(Yan et al., 2019a), *NKILA*(Huang et al., 2018), and *SOX5*(Wu et al., 2017) drive immune inefficiency/cancer progressionbypromoting apoptosis and exhaustion of T cells in the host. On the other hand,*RUNXOR*(runt-related transcription factor-1 overlapping RNA)(Tian et al., 2018a), *Olfr29-ps1*(Shang et al., 2019b), and *CHOP* (C/EBP-homologous protein)(Gao et al., 2018a) promote the differentiation and immunosuppressive/pro-canceractivity of MDSCs. LncRNA like *POU3F3* (Xiong et al., 2015) and *INSR* (Wang et al., 2018) directly enhances T-reg differentiation and

maintaining immunosuppressive microenvironment by promoting M2 polarization of tumor-associated macrophages (TAM), differentiation of CAF, secretion of IL10, TGF-b& IL-35, which abolish the anti-tumor activity of CD8+ cytotoxic T lymphocytes. Pre-clinical studies with cancer immunotherapeutic strategies inhibiting *NEAT1* have rescued cytotoxic potential and decreased apoptosis of CD8 T cells (Yan et al., 2019a). In the same line,studies with LINK-A (long intergenic non-coding RNA for kinase activation)inhibitors in pre-clinical models have also shown increased CD8 T cell infiltration and decreased cancer progression(Hu et al., 2019) by rescuing the expression of TAP1 and TAP2 proteins for improved phagocytosis and presentation of tumor antigen.However, some of the LncRNA like *SMAD3* have dual fate onT-reg differentiation and T cell activation (Xia et al., 2017).

TAMs are a critical component of the tumor micromilieu, and their index largely dictatesthe prognosis of the tumor(DeNardo and Ruffell, 2019). Recent studies have demonstrated the significant roles of LncRNA in the polarization of TAM mainly via STAT3 linked signaling pathways,*LncRNA-M2*, which drives M2 polarization via PKA/CREB axis is one common example (Chen et al., 2020). Furthermore, several ncRNAs like*GNAS-AS1* (guanine nucleotide-binding protein, alpha stimulating activity polypeptide-antisense RNA 1) (Li et al., 2020b; Liu et al., 2020), *XIST*(X-inactive specific transcript)(Sun and Xu, 2019) and *MM2P* (modulator of macrophage M2 polarization) (Cao et al., 2019) mediateM2 polarization of TAM in tumor micromilieu. Other ncRNA like *NIFK-AS1* (nucleolar protein interacting with the FHA domain of MKI67-antisense RNA 1), however, inhibit M2 polarizationby enhancing Notch1 (Notch homolog 1) or Jag1 (Jagged1) pathways,as seen in endometrial cancer (Zhou et al., 2018). Compelling studies suggest that inhibiting the expression of *LncRNA-P21* promotes M1 polarization (Zhou et al., 2020) and reduces tumor

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development.Paradoxically LINC00662 promotes WNT3A secretion by tumor cells which drive M2 polarization via the Wnt/β-catenin axis (Tian et al., 2020). Experimental evidence indicates that *MALAT1/NEAT2* silencing destabilizes*miR-140*(Hou et al., 2020) andenhances the anti-cancer immunity of the host by promotingM1 polarization, attenuating IL-10 secretion and concomitant M2 polarization in HCC. Another set of lncRNA, like *CASC2c*(cancer susceptibility candidate 2c),suppresses the M2 polarization and represses cancer progression (Zhang et al., 2018).

Apart from TAM, MDSCs also contribute to forming an immunosuppressive shield that escorts tumor cells forimmune evasion and refractoriness towardsimmunotherapy. Like TAM, they secrete angiogenic peptides like VEGF, MMP9 (matrix metalloprotease 9), etc., and help in cancer progression/metastasis (Shojaei et al., 2009; Tartour et al., 2011). Among various cytokines, IL-6 is a hybrid cytokine that promotes Th2/17 programming of the tumor micromilieu. This is due to its potential to up-regulate *LncRNA-RNCR3*(retinal noncoding RNA 3)(Shang et al., 2017), *CHOP*(Gao et al., 2018a), and *LncRNA-C/EBPβ* (antisense LncRNA transcribed from the reverse strand of C/EBPβ), which promote differentiation and immunosuppressive activities of myeloid populations within tumors. *LncRNA-C/EBPβ* silences C/EBPβ (CCAAT/enhancer-binding protein) and affects the expression of *Arg-1* (arginase1), *NOS2* (Nitric oxide synthase 2), *COX2* (cyclooxygenase-2), *NOX2* (NADPH oxidase 2), and IL-4, thus driving differentiation of MDSC into PMN-MDSC (polymorpho-nuclear), which further promote tumor development in TGF-β dependent manner (Gao et al., 2018b, 2019). In this direction, silencing these tumorigenic LncRNA has been shown to rescue anti-tumor potential of T cells. Depletion of *LncRNA-PVT1* jeopardizes the pro cancerous potential of PMN-MDSC

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byregulating c-Myc downstream signaling(Zheng et al., 2019). In this context, expression of HOTAIRM1(HOXA Transcript Antisense RNA, Myeloid-Specific 1)(Tian et al., 2018b) and RUNXOR have been shown to influence the polarization of tumor infiltrating myeloid cell populationspositively (Tian et al., 2018a) in a variety of tumors

Besides macrophages, tumor-associated neutrophils (TAN) also participatein constituting pro-inflammatory micromilieu of tumorsby secreting IL-6, IL-8, IL-12, and NET (neutrophil extracellular trap). lncRNA like *Gm43181* induces the expression of *CXCR2*, both recruit and activate neutrophils for inducing immunogenic inflammation (Zhang et al., 2019). On the contrary, *MALAT1* dampen the inflammation by downregulating the expression of IL-8, facilitating the recruitment and activation of neutrophils (Wei et al., 2019).*LncRNA-XIST* downregulates IL-12A and attenuates the formation of NET (Li et al., 2020a). Expression of *lncRNA-TCL6*(T-cell leukemia/lymphoma 6) has beencorrelated with TAN infiltration and poor survival of cancer patients (Zhang et al., 2020a). Up-regulated *lncRNA-HOTTIP*(HOXA transcript at the distal tip)in ovarian cancer triggersIL-6 response, up-regulates the secretion of PD-L1 (Programmed death-ligand 1) in TAN and promotes tumor immunesurveillance(Shang et al., 2019a).In addition to neutrophils,CD16/32+ immatureDC (dendritic cells)/CD141+DC have promotedcancer progression. Animal studies have demonstrated thatsilencing of lncRNA-DC abort maturation of DC and their Th1 priming ability(Wang et al., 2014) and promote Th2 priming ability.

Most tumors are heavily infiltrated with Treg,which is known to weaken T cell effector responses. This is mediated and manifested with CTLA4A(cytotoxic T-lymphocyte associated protein 4), IL-10, TGF-β, and adenosine expression, which inturn suppresses anti-cancer T cells, DC, and NK cells (Roncarolo et al., 2006; Wang et

al., 2011). *LncRNA-FLICR*(Foxp3 long intergenic noncoding RNA) represents one category of ncRNA (Zemmour et al., 2017),which negatively regulates *FOXP3*(forkhead box protein P3) expression, which is the main marker of both Tregs. Similarly, *LncRNA-FENDRR*(FOXF1 adjacent non-coding developmental regulatory RNA) (Yu et al., 2019) and *LncRNA-SNHG1*(small nucleolar RNA host gene 1) (Pei et al., 2018) prevent the differentiation of Treg and abolish immune evasion potential of tumors. Furthermore,*LncRNA-CD160* can impair the secretion of TNF-α and IFN-γ by CD8+CTLin hepatitis B virus infection (Wu et al., 2020) induced cancers.Several LncRNA like *SNHG14*(Zhao et al., 2019), *MALAT1*(Wang et al., 2019a), *LINC00473*(Zhou et al., 2019), etc., are found to be involved in the regulation of T cell apoptosis via the PD-1/PD-L1 axis.

Conclusion and major perspective

By utilizing the knowledge of non-coding RNA, Personalizeds immunotherapy can harness many benefits from currently available techniques like RNA destabilizing

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elements (RDEs) like poly(A) signals; blocking LncRNA promoter; transcript degrading; transcript silencing; inhibitors which can interfere with LncRNA interaction with the target; aptamers; gene editing/regulating tools like CRISPR, CRISPRi, and CRISPRa; and synthetic mimics(Zhang et al., 2020b). This knowledge can be currently used at its best in combinational cancer immunotherapy regimes like immune checkpoint blockade (ICB) therapy and chimeric antigen receptor T cell therapy (CAR-T). Integrating these tools with the findings as discussed above can yield very novel and specialized therapeutic interventions. For example, in a mice study, *LncRNA-NKILA*, which turns T cell sensitive to AICD, was targeted with shRNA showed positive results, overcoming immune evasion and AICD (Huang et al., 2018). Similarly, *LncRNA-INCR1* increased the cancer cell susceptibility to cytotoxic T cells and increased the efficacy of CAR-T treatment by controlling IFN-γ signaling(Mineo et al., 2020).

However, there are several limitations in this direction, as the difficulties with specific delivery of these molecules, with nano-particle mediated delivery and exosome-mediated delivery as the only options available. Besides this, the unstable structure, poorly conserved nature, which means the animal studies developments cannot be implemented on humans, and unknown side effects of LncRNA contribute to major roadblocks (Zhang et al., 2020b). So far, the knowledge we have in this direction is very naïve and preliminary, therefore seeks answers to many questions. However, LncRNA can be considered for combinational therapy with drugs and therapeutic antibodies used in cancer therapy(Sharma et al., 2020). Using/targeting these LncRNA according to their pro-cancer/anti-cancer roles can potentially manipulate the sensitivity of cancer towards chemotherapeutic drugs (Jiang et al., 2019), radiotherapy, and monoclonal antibody (Wang et al., 2019b).

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Legend to figure

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