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# The tumor microenvironment and radiotherapy response; a central role for cancer-associated fibroblasts

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A B S T R A C T

Tumor growth is not only dictated by events involving tumor cells, but also by the environment they reside in, the so-called tumor microenvironment (TME). In the TME, cancer-associated fibroblasts (CAFs) are often the predominant cell type. CAFs were long considered to be of limited importance in the TME, but are now recognized for their pivotal role in cancer progression. Recently, it has become evident that different subsets of CAFs exist, with certain CAF subtypes having protumorigenic properties, whereas others show more antitumorigenic characteristics. Currently, the intricate interaction between the different subsets of CAFs with tumor cells, but also with immune cells that reside in the TME, is still poorly understood. This crosstalk of CAFs with tumor and immune cells in the TME largely dictates how a tumor responds to therapy and whether the tumor will eventually be eliminated, stay dormant or will progress and metastasize. Radiotherapy (RT) is a widely used and mostly very effective local cancer treatment, but CAFs are remarkably RT resistant. Although radiation does cause persistent DNA damage, CAFs do not die upon clinically applied doses of RT, but rather become senescent. Through the secretion of cytokines and growth factors they have been implicated in the induction of tumor radioresistance and recruitment of specific immune cells to the TME, thereby affecting local immune responses. In this review we will discuss the versatile role of CAFs in the TME and their influence on RT response.

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## 1. Introduction

For decades cancer research has mainly been focused on cell intrinsic mechanisms of carcinogenesis, especially after the discovery of tumor suppressor genes and oncogenes [1]. However, already in 1889 the "seed and soil" hypothesis was proposed by Stephen Paget suggesting that elements of the stroma were important for tumor development [2]. He suggested that metastasis is not due to random events, but rather that some tumor cells (the "seeds") grow preferentially in selected organs (the "soil") and that metastases only appear when the appropriate seed was implanted in its suitable soil. This hypothesis is now confirmed by an extensive body of experimental research and clinical data [3]. There has been an appreciable increase in our understanding of the crosstalk that occurs between malignant cells and their organ microenvironment on the molecular, cellular and systemic level [3]. The variety of immune cells, stromal cells such as fibroblasts and pericytes, secreted factors, extracellular matrix (ECM) proteins and the vasculature in the tumor forms the so-called tumor microenvironment (TME) [4] (Fig. 1A). The TME does not only influence tumor cell proliferation, invasion and metastasis of cancer cells, angiogenesis, regulation of immune cell infiltration and the immune response, but also has an impact on the therapy response [5]. We here discuss the cellular and molecular cross talk between cells in the TME and radiotherapy response with a special focus on cancer associated fibroblasts (CAFs).

## 2. Cancer-Associated Fibroblasts

Fibroblasts can be considered as the weeds of the body, as they can survive harsh conditions that usually kills other cells. Because they can survive severe stress, including chemotherapy and radiotherapy, CAFs may represent a resistant cell type that can actively contribute to tumor relapse [6]. CAFs are recognized to be of critical importance in cancer progression [7–9], and in multiple solid tumors the presence of CAFs has been associated with poor prognosis [10]. CAFs are a prominent cell type in the TME and, next to cancer cells, constitute the majority of cell populations present in many solid cancers, including head and neck squamous-cell carcinoma (HNSCC), where late-stage HNSCC for example frequently consists of up to 80% of CAFs [11–13]. CAFs can originate from var-

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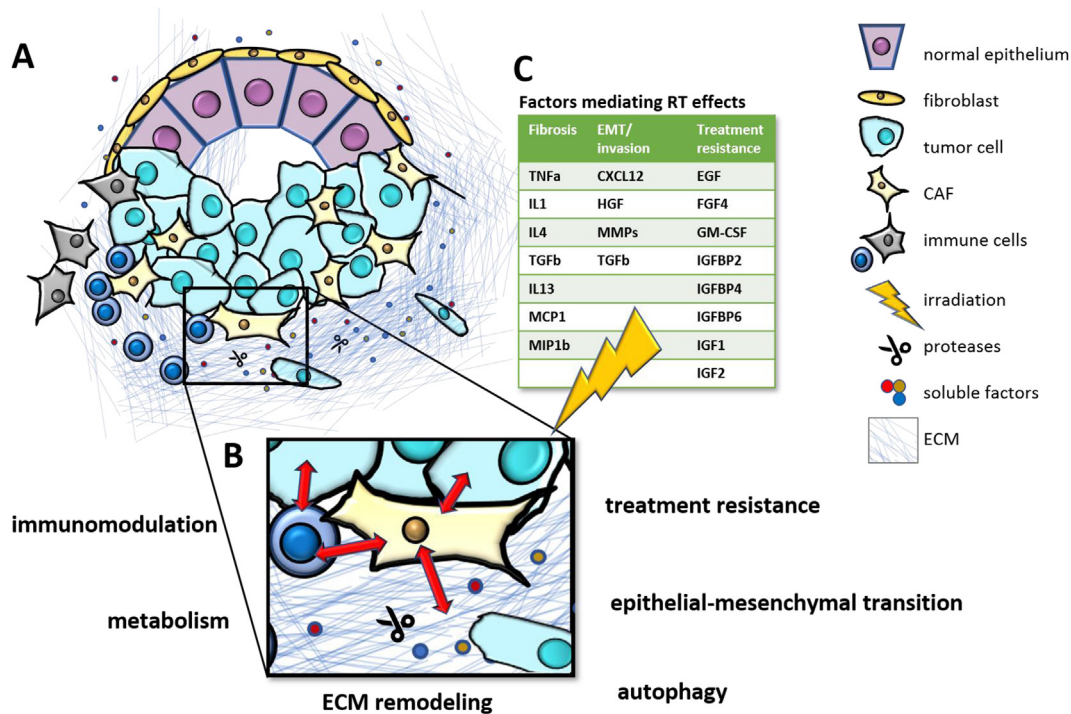  *E-mail address:* marleen.ansems@radboudumc.nl (M. Ansems).

**Fig. 1.** Cancer Associated Fibroblasts in the Tumor Microenvironment and therapy response A) CAFs play a central role in the TME by interacting with cancer cells and immune cells and affecting key processes such as B) immunomodulation, metabolism, ECM remodeling, autophagy, epithelial-mesenchymal transition and treatment resistance to e.g. C) radiation therapy. Different factors expressed by CAFs after RT mediate subsequent fibrosis, EMT/invasion and treatment resistance [126,131–133].

ious cell types including resident fibroblasts, bone marrow-derived mesenchymal cells, adipocytes, endothelial cells and stellate cells [14]. This can differ between stages of tumor initiation and progression, but also between tumor types [14–16]. In multiple solid tumors the intratumoral CAF population consists of different subsets that can respond differently to a variety of stromal stimuli, display distinctive secretory phenotypes and execute specific biological functions in the TME [17–26]. Currently, there is not yet a universal nomenclature used for the different subsets, but ongoing efforts for this are emerging [27]. CAFs or their specific subsets are generally characterized by expression of α-smooth muscle actin (α-SMA), Fibroblast activation protein-α (FAP), S100 calcium-binding protein A4 (S100A4 or FSP1) and Platelet-derived growth factor receptor alpha/beta (PDGFRα/β). Many of these markers are, however, also present on normal (activated) fibroblasts or other cells types [6,17,28,29], but together with the absence of epithelial, endothelial and immune cell markers such as Platelet endothelial cell adhesion molecule (PECAM-1 or CD31), cytokeratin and CD45 (Protein tyrosine phosphatase, receptor type, C), CAFs can be identified [13,17,30].

In the TME, CAFs have been demonstrated to influence many aspects of tumor biology. Most studies describe CAFs as producers of cytokines, chemokines, enzymes, metabolites and ECM (extracellular matrix) molecules [14]. Interestingly, CAFs are often found to have pro-tumorigenic properties by secreting growth factors (e.g vascular endothelial growth factor (VEGF), epidermal growth factor (EGF) and insulin-like growth factor (IGF), cytokines (e.g Interleukin (IL)-6, tumor-necrosis factor alpha (TNF-α) and Transforming Growth Factor beta (TGF-β) and chemokines (e.g C-X-C motif chemokine (CXCL) 1, CXCL2 and CXCL12) fostering tumor growth [31–36]. Other reports, however, have also attributed anti-tumorigenic characteristics to them; for example, they are suggested to form a physical barrier to restrict tumor cell growth and migration [37], and targeting the stroma can lead to immunosuppression, angiogenesis and worse survival [38–40].

CAFs are also known to be actively involved in the generation of desmoplasia; the growth of fibrous or connective tissue [41,42]. In the TME, CAFs are the major cell type responsible for the synthesis of ECM proteins such as collagens, laminin, tenascin C, fibronectin, but also many matrix metallopeptidases (MMPs) [6,43]. Interestingly, many immunosuppressive signaling molecules (e.g. VEGF and TGF-β) are matrix-bound and can be liberated from the ECM through MMPs [44,45], thus in addition to being secreted by CAFs, also the release of immunosuppressive molecules from the ECM mediated by CAF-secreted MMPs can contribute to the immunosuppressive TME. CAFs thus play a key role in remodeling the ECM. While the matrix architecture has long been considered to simply provide the structural framework of connective tissues, it is now recognized that it plays a key role in cancer cell survival and proliferation [46] and in facilitating or suppressing antitumor immune surveillance [47]. By remodeling the ECM, CAFs can also contribute to the increased mechanical stress that is generated in the TME, which can lead to compression of blood and lymphatic vessels, reduction of the perfusion rate and thus drug delivery, but also induction of hypoxia, promoting a more aggressive cancer phenotype [27,48].

Because CAFs can produce many different cytokines, chemokines, growth factors, ECM molecules, metabolites, miRNAs and exosomes they can influence cancer cells as well as other cells present in the TME, including immune cells (Fig. 1B).

## 3. CAFs and tumor cells

The interplay between cancer and stromal cells in the TME is recognized as a major driver of tumor progression and metastasis [49]. System-wide analyses have shed light on the complex tumor-fibroblast interactions that are involved in tumorigenicity [50]. This bilateral interaction of CAFs and tumor cells can oppose, but also synergize each other's function [14,28]. Especially the

paracrine signaling between CAFs and cancer cells, where CAFs produce different growth factors, chemokines and cytokines, can lead to tumor growth, cancer invasion and metastasis [14,33,51–57]. The crosstalk between cancer cells and CAFs in the TME also leads to metabolic reprogramming that contributes to activation of CAFs and cancer progression [58]. Interestingly, CAFs have been shown to co-travel with tumor cells in the blood [59]. By bringing their own "soil" cancer cells facilitate their own survival and extravasation to metastatic sites [59]. After the uptake of tumor-derived exosomes also resident fibroblasts can be involved in preparing a premetastatic niche [60] and vice-versa CAF-derived exosomes are able to reprogram the metabolic machinery of tumor cells and enhance tumor growth by transferring metabolites, including amino acids, lipids and TCA-cycle intermediates to tumor cells [61].

## 4. CAFs and immune cells

Initially, it was believed that cancer immune evasion was dependent on cancer cells, however increasing evidence shows that also CAFs can fuel immune escape in the TME [44]. CAFs can use a wide range of mechanisms to alter the anti-tumor immune response. They can affect the anti-tumor immune response by i) influencing the recruitment of immune cells, ii) drive an immunosuppressive function in, in particular, immune cells, iii) remodel the ECM to induce an immunosuppressive microenvironment and iv) directly inhibit the killing by cytotoxic lymphocytes [62]. Hereby CAFs can attract, retain and affect multiple immune subsets into the TME, including macrophages, Dendritic cells (DCs), Myeloid Derived Suppressor cells (MDSCs), Natural Killer (NK) cells and different subsets of T cells. Emerging evidence now support the hypothesis that this is not a unidirectional effect. Tumor infiltrating immune cells can also alter the stromal compartment, emphasizing a high degree of crosstalk between stromal and immune cells [63].

### 4.1. Macrophages

In the TME, macrophages and especially the subset of M2 macrophages are described to be major drivers of a tumor-supporting and immunosuppressive environment in tumors, including activation of stromal cells [63,64]. Synergistically, CAFs and tumor associated macrophages have been associated with prognostic significance in multiple types of cancer [65–68]. Cell-cell interaction between these two cell types can induce the recruitment and activation of each other, and their combined activities contribute to tumor progression [68]. By secretion of CXCL12, Granulocyte Macrophage Colony-Stimulating Factor (GM-CSF) and IL-6, CAFs can actively polarize resident macrophages towards the more protumorigenic M2-phenotype [67,69,70]. Reciprocally, TAMs with a M2 phenotype further activate CAFs and thereby promote tumor progression [71].

It has also been postulated that via the modification of the ECM CAFs can influence the presence of macrophages in the TME. CAFs are able to synthesize ECM components such as collagen type I, II and IV, but they can also express proteases like FAP, which by cleaving type I collagen alters ECM composition. It has been demonstrated that macrophages are not able to attach to native collagen type I, but they can bind to FAP-cleaved collagen type I through the scavenger receptors they express on their surface [72]. The expression of FAP was positively correlated to the number of macrophages in the tumor stroma [72]. Thus, by modifying the ECM CAFs enhance the recruitment and retention of macrophages in the TME and probably potentiating their biological functions. Overall, the interaction of CAFs and TAMs seems to be

reciprocal and triggered by cancer cells to favor the establishment of an immunosuppressive microenvironment.

### 4.2. Dendritic cells

DCs are the most important antigen-presenting cells that have a pivotal role in activation of T cell-mediated anti-tumor immunity. It has been reported that hepatic carcinoma derived CAFs induce Indoleamine 2,3-dioxygenase (IDO)-producing, regulatory DCs, thereby inducing higher number of T regulatory (Treg) cells, resulting in a decreased anti-tumor response [73]. CAFs are also a major producer of TGF-β [51,74]. TGF-β can affect DC development, activity and motility and in general DCs acquire a regulatory phenotype in the presence of TGF-β [75–77]. Fibroblast-produced IL-6 is reported to favor the differentiation of monocytes into tumor associated macrophages at the expense of differentiation into DCs [78]. IL-6 however also directly influences DC function; IL-6-mediated activation of the Signal transducer and activator of transcription 3 (STAT3) pathway affects DC maturation, disabling T cell activation and subsequently inducing T cell anergy and immune tolerance [79–81]. Next to IL-6 and TGF-β, CAFs also produce VEGF [82,83]. This may not only affect angiogenesis, but may also alter DC function as VEGF has been shown to suppress its generation and maturation [84–86].

### 4.3. Myeloid Derived Suppressor Cells

MDSCs form a heterogeneous population of immature myeloid cells that suppress T cell function and promote tumor angiogenesis, tumor progression and metastasis [87,88]. By secreting factors such as CXCL12, IL-6 and chemokine (C–C motif) ligand 2 (CCL2), CAFs have been shown to drive differentiation of monocytes into MDSC as well as attract them to the TME [89–91]. Recently it has been shown that CAFs can also promote immunosuppression by inducing Reactive Oxygen Species (ROS) -generating monocytic MDSC in lung squamous cell carcinoma [92].

### 4.4. Natural Killer cells

NK cells are innate immune cells that have cytotoxic effector functions [93]. CAFs can modulate the activation of NK cells in the tumor stroma. CAFs derived from endometrial cancer have been shown to significantly reduce NK killing activity by direct cell-to-cell contact [94]. Compared to normal fibroblasts, CAFS have a lower expression of the Poliovirus receptor (PVR/CD155), which is a ligand for the NK activating receptor DNAX Accessory Molecule-1 (DNAM-1). By downregulating CD155, CAFs attenuate NK cell-killing activity [94]. Also, Prostaglandin E2 (PGE2) and MMPs released from CAFs significantly impairs the ability of NK cells to recognize and kill tumor cells [95–97]. CAFs can thus inhibit the activity of NK cells against tumor development directly through cell-to-cell contact and indirectly by the secretion of soluble factors [93,98].

### 4.5. T Cells

The interaction between CAFs and T cells has been demonstrated by multiple studies *in vivo* and *in vitro*. Distinct subpopulations of CAFs have been shown to exhibit immunosuppressive functions through affecting attraction, survival, migration, function and differentiation of different subsets of T cells in multiple types of cancer [18,99–102]. CAFs can do this by secretion of different cytokines and chemokines such as IL-6, CXCL12 and IL-1β, by the release of nitric oxid (NO), but also by expression of molecules such as OX40-ligand (OX40L), Programmed death ligand 2 (PD-L2), Junctional adhesion molecule B (JAM2), B7H3, Dipeptidyl

peptidase-4 (DPP4) and ecto-5′-nucleotidase (CD73) [18,99–102]. Interestingly, CAFs have also been demonstrated to express MHCII molecules [20,103] a characteristic of antigen presenting cells (APCs). Via expression of MHCII molecules together with the expression of costimulatory molecules such as CD80 and CD86, professional APCs can activate T cells and initiate an antigen-specific immune response. MHCII expression in the absence of expression of costimulatory molecules leads to activation of Tregs and thus to suppression of an immune response. As CAFs typically do not express costimulatory molecules [20,103] it suggests that CAFs induce activation of Tregs. Also normal colonic myofibroblasts have been shown to express MHCII and this expression was essential for the induction of Tregs. The authors postulate that in the normal colon the colonic myofibroblasts contribute to the suppression of active inflammation by supporting expansion of Tregs [104].

Localization and migration of T cells is dependent on the specific tissue architecture; in loose fibronectin there is active T cell motility, whereas T cells migrate poorly in dense matrix areas [105]. The composition of the ECM can thus influence antitumor immunity by controlling the positioning and migration of T cells [106]. By remodeling the ECM, also CAFs can influence T cell migration and trap T cells in the stroma by forming a physical barrier limiting access to tumor cells [44,107,108]. CAFs can also affect T cell function and activation by the release of the ECM protein βig-h3. The presence of βig-h3 reduces antigen-specific activation and proliferation of CD8 + T cells [109]. Interestingly, CXCL12 secreted by FAP-expressing CAFs has also been suggested to prevent effector T cells from reaching cancer cells. CXCL12 secreted by CAFs localized on cancer cells and when the ligand for CXCL12, (chemokine (C-X-C motif) receptor 4 (CXCR4)), was inhibited, T cells accumulated again to the tumor [110]. The immunosuppressive effect of CAFs may thus be partly mediated via CXCL12-mediated T cell exclusion from the tumor.

CAFs directly isolated from multiple human tumors are shown to express the PD-1 ligands PD-L1 and PD-L2 [107,111,112], suggesting direct suppression of T cells. Another way how CAFs can suppress T cells is via the production of metabolites such as adenosine and lactate [113,114].

Taken together, this demonstrates the role of CAFs as important inhibitors of T effector mediated immune responses against tumors and simultaneously as potent activators of Treg functions.

## 5. CAFs and radiotherapy

Radiotherapy (RT) is an effective and widely used local cancer treatment, with a majority of cancer patients undergoing RT at one point during treatment. Although primarily directed at killing tumor cells, RT also affects the TME, including the immune cells, endothelial cells, vasculature and fibroblasts, with important consequences for tumor growth, -dissemination, and -control. RT is given in different doses and treatment fractions based on tumor type as well as to reduce normal tissue toxicity. How these different treatment schedules influence the TME is, however, largely unknown. Many different mechanisms have been described whereby RT via the TME, and in particular CAFs, influences tumor growth and treatment sensitivity.

CAFs are particularly radioresistant as they do not die upon RT, but rather go into senescence [115,116]. Indeed, irradiation of CAFs has been shown to cause persistent DNA damage [116,117], and to induce a senescence response [116,117] and specific changes in the secretory profile (e.g. CXCL12, TGF-β1, IGF-1, IGFBP2 and NO) [117–125]. Notably, RT-mediated TGF-β signaling induces activation of (peri)tumoral fibroblasts to CAFs and their proliferation in the TME, which enhances the CAF mediated effects on the tumor.

The altered phenotype of the CAFs subsequently induces an altered metabolic profile [121], and is associated with epithelial-to-mesenchymal transition [118] and changes in invasiveness [118,119] of the associated tumor cells. This plethora of RT-induced changes in the interaction between tumor cells, immune cells, and the TME has particular consequences for the tumor's sensitivity for treatment.

## 6. CAFs and sensitivity to RT

RT can induce antitumor immune responses, although in general this does not lead to the much-desired abscopal effect where the RT-induced immune response has systemic effects on distant metastases. The generally immunosuppressive TME may counter the RT-induced immune response. As mentioned above, RT also promotes activation of CAFs and thus modulates the behavior of the TME for the response to RT (Fig. 1C) [126]. After RT, the TME activates a number of pathways and mechanisms that may subsequently be associated with tumor radioresistance, which can be through secretion of cytokines, growth factors, exosomes, and ECM remodeling factors [127,128]. The interactions between fibroblasts/ CAFs and cancer cells are bi-directional and promote tumor growth, cancer invasion, metastasis, and therapy resistance [129,130].

For example, by the activation of inflammatory pathways, RT induces fibrosis by different cytokines such as TGF-β1, TNF-α, IL-1, IL-4 and IL-13; chemokines such as MCP-1 and MIP-1β; angiogenic and growth factors [131–133]. Fibrosis in turn is associated with radioresistance by supplying signals to tumor cells leading to treatment resistance, proliferation and metastasis [134]. Additionally, activated CAFs can induce epithelial-to-mesenchymal transition [118], which may promote radioresistance via loss of e-cadherin [135]. Similarly, RT induces expression of both α and β integrins within the stroma [136,137]. This increased integrin expression induces chemoradiation resistance of tumors and induces tumor growth of multiple cancer types [138,139]. Furthermore, radiation resistance of prostate cancer cells could be linked to the loss of the membrane protein caveolin-1 in stromal fibroblasts [140–142]. Furthermore, in vivo CAFs can induce autophagy and subsequent irradiated tumor cell recovery [128]. Autophagy is either directly involved in radioresistance by modulating DNA damage repair [143] or indirectly by enabling cells to survive hypoxia [144], thereby inducing radioresistance.

Fibroblasts have been found to secrete exosomes containing 5′-triphosphate RNA to induce an IFN-related DNA damage resistance gene signature (IRDS) by activating RIG-1. Subsequent activation of STAT1 facilitated Notch signaling in breast cancer cells inducing a RT resistant stem cell-like phenotype [145]. This IRDS and STAT1 signaling have found to be associated with radioresistant breast cancer in vitro, in vivo and in patient cohorts [146,147]. Similarly, after multiple passages of the head and neck cancer cell line SCC-61 in irradiated mice, these became radioresistant. The resulting resistant SCC-61 cells exhibited the same IRDS in which STAT1 was demonstrated to be a key mediator of radioresistance [148].

Of note, Steer et al. tested the effect of different fibroblasts (NIH-3 T3 or L929) on several tumor cell lines in direct or indirect coculture, and found complex bi-directional direct and indirect interactions between cancer cells and fibroblasts with impact on tumor growth and therapy outcome. They found that the impact of fibroblasts on tumor cells radiation response largely depended on the fibroblast and tumor cell type, the culture conditions (direct/indirect co-culture) and the respective endpoint (short-term vs. long-term; in vitro vs. in vivo [149]. This is likely caused by the fact that tumor cells and RT influence fibroblast phenotypes, with important repercussions for the reciprocal interaction

between CAFs and tumor cells, which makes interpretation of many, especially preclinical, experimental data difficult.

## 7. Perspectives

Although CAFs have long been ignored in cancer biology, their essential role has received more attention the last decade. CAFs affect multiple steps in cancer development, progression, metastasis and (radio)therapy response and are therefore a promising target in cancer therapy. However, general depletion of CAFs is likely not a good strategy for enhancing cancer therapy response, as pro-tumorigenic as well as anti-tumorigenic properties are ascribed to them. This is evidenced by the contradictory results found when targeting the tumor stroma [14,32,38,39,134,150]. For CAF targeting to become a viable option, the specificity of markers to identify CAFs and their heterogeneity should be considered. Currently, several preclinical strategies are ongoing that target specific actions or subpopulations of CAFs [17,44,86]. Additionally, radiotherapy schedules that enhance anti-tumorigenic and/or attenuate protumorigenic functions of CAFs and immune cells may be identified, thereby enhancing radiosensitivity of solid tumors. Future studies that further decipher the complex tripartite interaction between CAFs, cancer cells and immune cells will provide a more solid base for the design of more effective (combinatorial) therapeutic strategies against cancer.

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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