Role of tissue Transglutaminase in glial cell processes involved in multiple sclerosis
Espitia Pinzón, N.

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Summary

MS is a chronic neuroinflammatory, demyelinating disease (Noseworthy, 1999; Noseworthy et al., 2000) mainly affecting young adults (Weinshenker et al., 1989). Various pathological processes take place in MS including infiltration and migration of leukocytes (McCandless et al., 2008; Aubé et al., 2014; Ortiz et al., 2014) into the CNS, astrogliosis (Axelsson et al., 2011; Hostenbach et al., 2014) and failure of remyelination (Kuhlmann et al., 2008; Stoffels et al., 2013a). This results in permanent neurodegeneration (Friese et al., 2014; Mahad et al., 2015) and progressive clinical symptoms (Willis and Fox, 2016). Considerable improvements have been made in MS therapeutics (Weber, 2012; Feinstein et al., 2015; Correale et al., 2017), elucidation of pathogenesis (Trapp et al., 1999; Gold et al., 2006) and genetics (Cree, 2014). However, no cure exists and no recognized definite cause, be it genetic, microbial or environmental has been identified (Høglund and Maghazachi, 2014). It is therefore essential to continue the efforts to characterise molecular and cellular events that underlie the neuropathological processes occurring during MS.

TG2 is a well-characterised multifunctional protein (Gundemir et al., 2012) that is expressed in the CNS (Johnson et al., 1997a; Lesort et al., 2000). TG2 is induced by e.g. inflammation (Kim, 2006) and is involved in processes that are important in the neuropathology of MS, such as cell adhesion and migration (Akimov and Belkin, 2001a; Png and Tong, 2013), and cell differentiation (Numinskaya and Belkin, 2012). Moreover, TG2 is able to bind and crosslink several ECM proteins (Collighan and Griffin, 2009), where its interaction with fibronectin is best characterised (Turner and Lorand, 1989). We therefore hypothesised that TG2 is implicated in various pathological processes occurring during MS (see Figure 1). In the present thesis we focused on the expression and role of TG2 in animal and cell models mimicking inflammation, astrogliosis, and/or de- and remyelination in MS. The overall aim of this thesis was to understand the relation between TG2 and (1) migration of infiltrating monocytes (chapter 2); (2) ECM protein fibronectin rearrangement (chapters 3 and 4); (3) differentiation of OPCs and subsequent myelination (chapter 5).

In chapter 2 we studied the expression of TG2 in white and grey matter lesions in the marmoset EAE model for MS. We observed the appearance of immunoreactive TG2 in monocyte and microglial-like cells in early active white matter, and active grey matter marmoset EAE lesions. When white matter lesions progress to late active and inactive stages, TG2 immunoreactivity is still present, though it is significantly less pronounced in the inactive lesions. Immunoreactive TG2 in monocytes in active white matter lesions during marmoset EAE, shows co-expression with β1-integrin and is in close association to extracellular fibronectin. In grey matter lesions, we found TG2 positive microglia that co-label with β1-integrin, but observed no fibronectin in these lesions. This strongly suggests an important role for TG2 in the adhesion, migration and/or differentiation of infiltrating monocytes in non-human primate EAE, and possibly MS.
With respect to the possible role of TG2 in fibronectin production and rearrangement, we studied expression and regulation of cellular TG2 and its function in relation to fibronectin. Astrocytes are important producers of ECM proteins, like fibronectin, and were therefore subject of our study. In Chapter 3 we demonstrated that TG2 expression and activity is enhanced during cuprizone-induced demyelination in astrocytes. Moreover, TG2 directly contributes to fibronectin production, and plays a role in fibronectin deposition during cuprizone-induced demyelination. In Chapter 4, we observed that in our in vitro experimental set-up, exogenous TG2 contributes to aggregation of fibronectin produced by astrocytes, whereas endogenously produced TG2 contributes to the appearance of morphological fibril-like fibronectin, but is not involved in fibronectin aggregation under inflammatory conditions. Our observations therefore imply that during MS lesion formation, when inflammatory mediators are present, astrocyte-derived TG2 may contribute to ECM rearrangement, and subsequent astroglial scarring. Overall, the results of the experiments described in Chapters 3 and 4 support the idea that TG2 contributes to the production, deposition and rearrangement of fibronectin during demyelination and inflammation.

In Chapter 5 we focused on the role of TG2 in the differentiation of OPCs and subsequent myelination. We found that TG2, either endogenously expressed, or exogenously supplied to OPCs, accelerated OPC differentiation. In addition, we observed TG2 immunoreactivity in OPCs during human development, but not in cells of the oligodendrocyte (OLG) lineage in MS lesions. Together with our previous data that TG2 activity is required for OPC differentiation, and that remyelination is delayed in TG2-/- mice (van Strien et al., 2011a), these results indicate that TG2 may have a regulatory role in the timing of early OPC differentiation.
Figure 1: TG2 is implicated in several important neuropathological processes that contribute to the disease course of MS. (A) TG2 supports adhesion, migration and differentiation of infiltrating monocytes. (B) TG2 also contributes to the production, deposition and rearrangement of fibronectin during demyelination and inflammation, thereby facilitating glial scar formation. (C) In addition, TG2 has a regulatory role in the timing of OPC differentiation, demonstrating the role of TG2 in (re)myelination. (TG2: tissue Transglutaminase, OLG: oligodendrocyte, OPC: oligodendrocyte progenitor cell)