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Phenotypic characterization of γδ T cells mobilized in response to acute psychological stress

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ABSTRACT

Gamma-delta (γδ) T lymphocytes are versatile cells that play key roles in bacterial clearance, wound repair, and delayed-type hypersensitivity reactions. Recently we showed that these cells are mobilized into the blood during acute psychological stress. γδ T lymphocytes are a heterogeneous population of cells, and the current study aimed to characterize the effects of stress on distinct γδ T cell populations.

Twenty-nine healthy participants completed a 12 min speech task. Blood samples were taken after a resting baseline, during the last two minutes of the task, and after a 15 min recovery period. Flow cytometry was used to investigate the response of memory phenotypes (i.e. Naïve, Central memory, Effector Memory, and CD45RA$^+$ Effector Memory (EMRA)) within the δ1 and δ2 γδ T cell populations. Cells were further analysed on expression of adhesion molecules (CD11a, CD62L) and the NK-receptor CD94.

Both the δ1 and δ2 subsets were mobilized during stress, and for both subsets, EMRA cells were mobilized to a much greater extent than the other memory phenotypes. Analysis of migration markers revealed that mobilized cells had a predominantly tissue migrating phenotype (CD11a^{hi}CD62L$^{lo/neg}$) and expressed high levels of the NK-receptor CD94.

The current findings indicate that stress primarily mobilizes γδ memory cells that have high cytotoxic capability, tissue homing potential, and the capacity for rapid, innate-like target recognition. This selective mobilization possibly provides protection in contexts when tissue damage and antigen exposure are more likely to occur.

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1. Introduction

The rapid mobilization of lymphocytes into the blood, known as lymphocytosis, is one of the best documented effects of stress on the immune system (Benschop et al., 1996; Segerstrom and Miller, 2004). This response is largely mediated by the effects of catecholamines on β-adrenergic receptors expressed on lymphocytes (Benschop et al., 1996; Elenkov et al., 2000). Accordingly, stress lymphocytosis is considered to be integral to the proverbial 'fight-flight' response, potentially preparing the immune system for an impending assault (e.g. wounding, infection) (Benschop et al., 1996; Dhabhar, 2002). Supporting this notion, animal studies have shown that stress-induced lymphocyte redistribution is associated with an enhanced immune defense, such as an increased delayed-type hypersensitivity reaction (Dhabhar and McEwen, 1996), an increased leukocyte migration into wounded tissue (Viswanathan and Dhabhar, 2005), and an enhanced response to immunization (Dhabhar and Viswanathan, 2005). These observations have been partly replicated in humans (Edwards et al., 2007), although how lymphocytosis may contribute to these beneficial effects remains to be determined. A more detailed phenotypic characterization of this stress response may help elucidate its possible role.

Meta-analysis indicates that stress preferentially mobilizes lymphocytes with cytotoxic functions, such as NK cells and CD8 T cells (Segerstrom and Miller, 2004). More recently, we found a third cytotoxic lymphocyte population, the gamma-delta (γδ) T cell, that is mobilized during psychological stress, as well as during exercise and beta (β)-agonist infusion (Anane et al., 2009). γδ T cells constitute approximately 5% of total T cells in the blood, yet comprise up to 50% of T cells in epithelial tissues, such as the skin and lining of the gastro-intestinal tract. Here, they form sentinel cytotoxic cells involved in a variety of immune processes (Carding and Egan, 2002; Girardi, 2006). These include the elimination of bacterial infection (Nakasone et al., 2007; Wang et al., 2001),

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delayed-type hypersensitivity reactions (Askenase, 2001), and wound repair (Girardi, 2006; Jameson et al., 2002), as well as having immunoregulatory and antigen presenting capabilities (Brandes et al., 2005; Morita et al., 2007).

The γδ T cells are divided into two major subsets: the delta 1 (δ1) and delta 2 (δ2) cells (Girardi, 2006). Both δ1 and δ2 T cells can be further separated into four memory phenotypes using the markers CD45RA and CD27 (Angelini et al., 2004; Caccamo et al., 2005; Dieli et al., 2003); this is comparable to the characterization of $CD8^+$ T cell memory classification (Hamann et al., 1997; Sallusto et al., 2004). The first phenotype comprises Naïve (NA) cells ($CD45RA^+$, $CD27^+$) which have never encountered their cognate antigen and lack cytotoxic effector functions. These cells express high levels of the adhesion molecule CD62L, which enables migration to the lymph nodes. The remaining three phenotypes are antigen experienced (i.e., memory cells), and are divided into Central Memory cells (CM; $CD45RA^-$, $CD27^+$); Effector Memory cells (EM: $CD45RA^-$, $CD27^-$); and $CD45RA^+$ Effector Memory cells (EMRA: $CD45RA^+$, $CD27^-$) (Angelini et al., 2004; Caccamo et al., 2005; Dieli et al., 2003; Sallusto et al., 2004). CM cells, like NA cells, express CD62L, indicating a lymph node homing potential, and lack immediate cytotoxic capability. In contrast, EM and EMRA cells express the adhesion molecule CD11a, which aids migration into sites of inflammation, and have downregulated CD62L (Angelini et al., 2004; De Rosa et al., 2004; Dieli et al., 2003; Sallusto et al., 2004). These effector-memory phenotypes also exhibit NK-like features (e.g., expression of CD94, a surface molecule involved in detection of aberrant MHC expression on infected and cancerous cells) (Angelini et al., 2004; Moretta et al., 1997), and have a greater cytotoxic capability than the NA and CM subsets (Angelini et al., 2004; Caccamo et al., 2005; De Rosa et al., 2004; Dieli et al., 2003; Hamann et al., 1997; Sallusto et al., 2004).

Recent research has demonstrated that EM and EMRA $CD8^+$ T cells are preferentially mobilized during adrenergic stimulation (Campbell et al., 2009; Dimitrov et al., 2009, 2010; Riddell et al., 2009), when compared to NA and CM phenotypes. These results are consistent with earlier findings that $CD11a^{hi}$ and $CD62L^{lo/neg}$ $CD8^+$ T cells are mobilized during stress and exercise (Goebel and Mills, 2000; Mills et al., 2003), and a similar pattern of adhesion molecule expression is seen on mobilized NK cells (Bosch et al., 2005; Goebel and Mills, 2000; Mills et al., 2003). The aim of the current study is therefore to perform a phenotypic characterization of γδ T cell subsets mobilized in response to psychological stress. Based on the above findings, it was hypothesized that γδ T cells expressing rapid response ability (i.e., an effector-memory phenotype), the capacity to migrate to inflamed tissue (e.g., $CD11a^{high}$), and an NK-like ability for target recognition (e.g., expression of CD94) will be preferentially mobilized. The two main γδ T cell subsets, δ1 and δ2, are known to exhibit distinct tissue preferences (Girardi, 2006), and therefore the effects on these subsets, and their memory phenotypes, were separately analyzed.

2. Methods

2.1. Participants

Twenty-nine university undergraduates (Mean age = 21.8 (SD = 2.2) years, 14 women) took part in this study. All participants reported being in good health and were non-medicated with the exception of the contraceptive pill. Participants were instructed not to engage in strenuous physical exercise and to refrain from consuming alcohol or non-prescription drugs 24 h before their experimental session, and to abstain from smoking and caffeine on the day of the experiment. Health and lifestyle information was obtained by self-report questionnaire. Blood was taken from an 18-gauge intravenous cannula (Becton–Dickinson) inserted into a palpable vein in the antecubital fossa. Cannulation was performed 20 min before the first blood draw ('baseline') and the same cannula was used for subsequent blood withdrawals. Participants provided informed consent and study protocols were approved by the University of Birmingham ethical review board. A small section of the data from this study has been presented elsewhere (Anane et al., 2009).

2.2. Procedures

Participants were tested between 9 am and 1 pm. Following instruction and instrumentation, participants completed a 20 min seated baseline during which questionnaires were completed. At the end of this period, a 'baseline' blood sample was obtained and the laboratory stressor was initiated. A second 'task' blood sample was obtained during the final two minutes of the social stress task, and a third 'Recovery' blood sample was taken 15 min post-task. The social stress task involved participants delivering two consecutive speeches, each with two minutes preparation and four minutes of delivery (Bosch et al., 2003a). To enhance social stress, speech tasks were performed in the presence of an audience of three confederates and videotaped. Recorded task instructions were presented on a computer screen in order to standardise instruction and timing. Affective responses were assessed with Profile of Mood States (POMS)(McNair et al., 1992), which was given at baseline, immediately post-task, and at the end of the recovery period. Instructions of the post-task questionnaire were adapted to reflect how the participants felt during the task. To assess autonomic nervous system activation, cardiovascular activity was recorded throughout.

2.3. Cardiovascular analysis

Indices of sympathetic and parasympathetic drive were obtained by analysis of electrocardiogram (ECG) and thoracic impedance (ICG) signals (Berntson et al., 1997; Sherwood et al., 1990). The ICG and ECG signals were recorded from six Ag/AgCl spot-electrodes (Conmed corporation, UTICA, NY, USA) using a VU-AMD device (Vrije Universiteit, Amsterdam, Holland). Reliability and validity of the VU-AMD device have been reported elsewhere (de Geus et al., 1995; De Geus and van Doornen, 1996; Willemsen et al., 1996). The ICG complexes were ensemble averaged with reference to the ECG R-wave across 1-min periods. From these 1-min ensembles, averages were computed for heart rate (HR), heart rate variability (RMSSD) and the pre-ejection period (PEP). These minute-by-minute means were averaged over the last 6-min of baseline, each 6-min speech, and the last 6-min of recovery. Changes in PEP were used to index changes in cardiac sympathetic drive (Sherwood et al., 1990), whereas RMSSD (Root mean Square of Successive Differences) was used to index changes in cardiac vagal tone (Bosch et al., 2003b; Goedhart et al., 2007). The RMSSD was log transformed to restore normality. Measurements of systolic and diastolic blood pressure (SBP and DBP, respectively) were taken at two minute intervals using an Omron M5 blood pressure monitor (Omron Healthcare UK Ltd., Milton Keynes, UK). Baseline, task and recovery values (10-min post-task onwards) were averaged and used in subsequent analyses.

2.4. Flow cytometry

Blood was collected in ethylene-diamine-tetraacetic acid (EDTA) coated vacutainer tubes (BD, BD Biosciences). Blood was kept at room temperature and prepared within 2 h. Lymphocyte subsets were identified by immunofluorescent antibody staining of whole blood using four-colour flow cytometry (FACS-Calibur,

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